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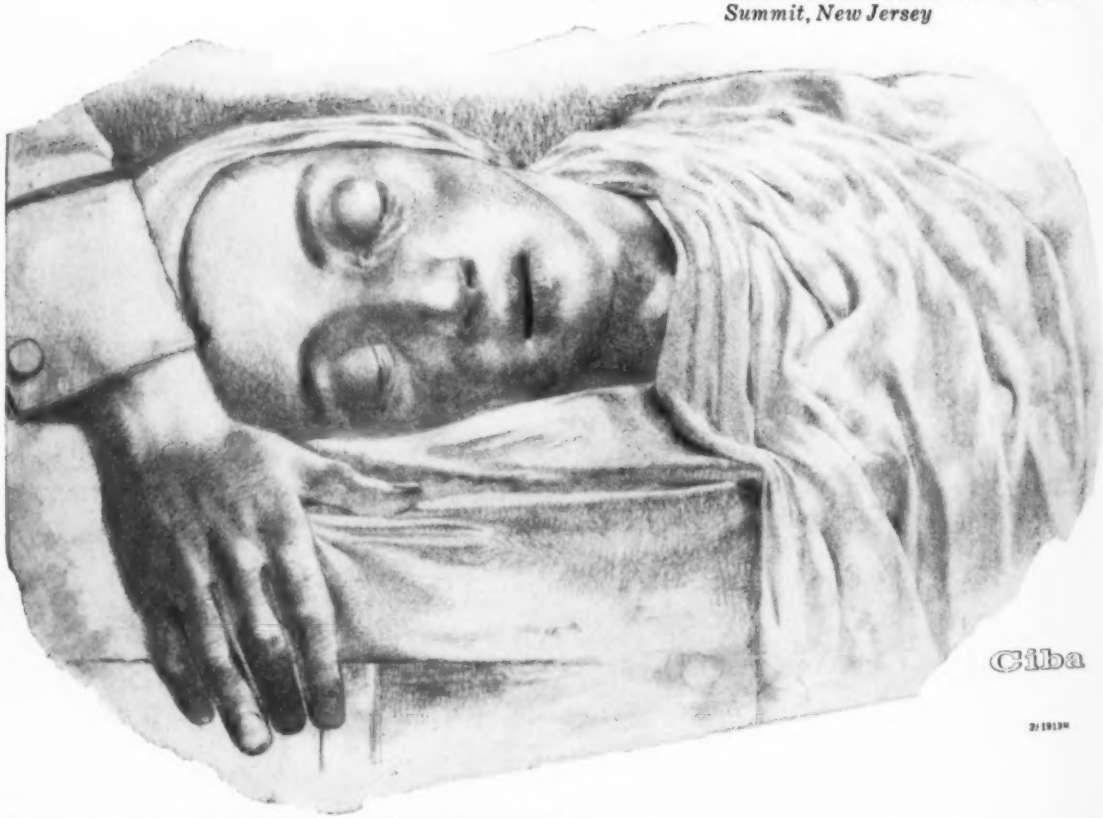

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THE PHOSPHOLIPID-CHOLESTEROL RELATIONSHIP IN HUMAN PLASMA: ITS IMPLICATIONS IN THE ATHEROSCLEROSIS PROBLEM

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That lipids are present in human plasma is certainly not news to the medical profession, but it is only in recent years that they have become newsworthy. Growing interest in the problem of atherosclerosis, and a change in attitude toward this disease, once considered an inevitable accompaniment of aging, have combined to produce the remarkable amount of work in this field which has characterized the last twenty years. Not a little of this effort has been expended on the lipids in plasma, because the lipids which are deposited in the intima and which are the hall-mark of atherosclerosis, appear to be derived from those in the plasma. Initially the emphasis was placed on cholesterol, since the diseases known to predispose to atherosclerosis were usually also characterized by a hypercholesterolemia, and since hypercholesterolemia induced in rabbits produced a disease which in many ways resembled atherosclerosis in man (1). This approach ignored the presence of other lipids in atheromata (2–6), as well as the abnormalities of other plasma lipids which occur under such clinical and laboratory conditions (7).

As time went on, it became evident that the level of circulating cholesterol was not a reliable index of atherogenesis. The demonstration of Hueper (8) of the production of atheroma-like lesions by means of physically similar but chemically different colloids led many to suspect that the crux of the problem might lie in the physical state of the cholesterol rather than its absolute amounts. In 1949 Ahrens and Kunkel (9) pointed out that the physical structure of the chief phospholipid of plasma, lecithin, was such as to make it possible for this molecule to act as a link between the hydrophobic lipids and the watery environment in which they are suspended. At one end of this molecule, there are lipophilic fatty-acid radicals; and at the other end, a hydrophilic phosphorylcholine group. Ahrens and Kunkel also pointed out that clear sera—*i.e.*, with

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highly dispersed lipids—were not necessarily low in lipid, as for example the clear serum seen in obstructive jaundice. When they produced a breakdown in the colloidal suspension of clear sera by enzymatic destruction of the lecithin, they seemed to have substantiated their thesis that the phospholipids can and do act as solubilizing agents for the more hydrophobic lipids such as cholesterol. They further noted that the ratio between phospholipid and cholesterol was high in obstructive jaundice (which they did not believe predisposed to atherosclerosis) whereas it was low, both as compared to normal sera and to the obstructive jaundice sera, in such diseases as nephrosis, hypothyroidism and essential xanthomatosis. Later in 1949, Kellner and his associates (10) reported experiments which suggested that failure of the phospholipid level to keep pace with the rise in the cholesterol level induced by dietary means in rabbits may be the crucial factor in the development of this type of experimental atherosclerosis.

Thus, it might be said that the phospholipid-cholesterol ratio was reborn, and the reports of Morrison (11) and of Gertler and Garn (12) quickly brought this new concept to the attention of clinical circles. Actually, the idea of this ratio was an old one, which had languished at the laboratory level for at least thirty years. Early workers had considered it a constant (13, 14), but the later results of Peters, Man and their colleagues threw considerable doubt on this when they found that the ratio varied with the level of the circulating cholesterol (15–17) and was markedly disturbed in patients with liver disease (18). Unfortunately, much of this work was apparently lost sight of in the later enthusiasm for this ratio.

In 1949, stimulated by the reports of Ahrens and Kunkel and of Kellner and his associates, we reviewed our results in a variety of disease states and found ourselves traversing much of the ground covered some ten years previously in Dr. Peters' laboratory. We learned that it was possible to demonstrate lower phospholipid-total cholesterol ratios in a number of diseases which were either due to atherosclerosis or predisposed to its development, but it quickly became evident that in many cases (*e.g.*, diabetes mellitus and myocardial infarctions) it was not a constant finding. A re-examination of the data suggested that this ratio could be a function of the cholesterol level, leading to the suspicion that, independent of the disease state, a basic relationship between phospholipid and cholesterol might be demonstrable. With this in mind, 242 determinations were abstracted from data collected in the course of previous work, using as a basis the diagnostic categories listed in Table 1. By using these multiple diagnostic groups, we hoped to eliminate the effect of any given disease on these lipids, and at the same time secure maximal variation in their values. Total and free cholesterol were determined by the method of Schoenheimer and Sperry (19). Lipid phosphorus was determined by the method of Fiske and SubbaRow (20), after extraction by the method of Boyd (21); this value was multiplied by the factor of 25, converting it to milligrams of "phospholipid" as lecithin.

When, as shown in Figure 1, these values for total cholesterol concentration were plotted against the corresponding phospholipid levels for each sample, a

TABLE 1

Diagnostic group	No. of determinations
1. Controls (normals)	102
2. Essential familial hypercholesteremia	49
3. Liver disease	31
4. Hypothyroidism	20
5. Nephrotic stage of nephritis	4
6. Essential hypertension	11
7. Diabetes mellitus	3
8. Coronary artery disease	3
9. Combinations of 2 through 8	19

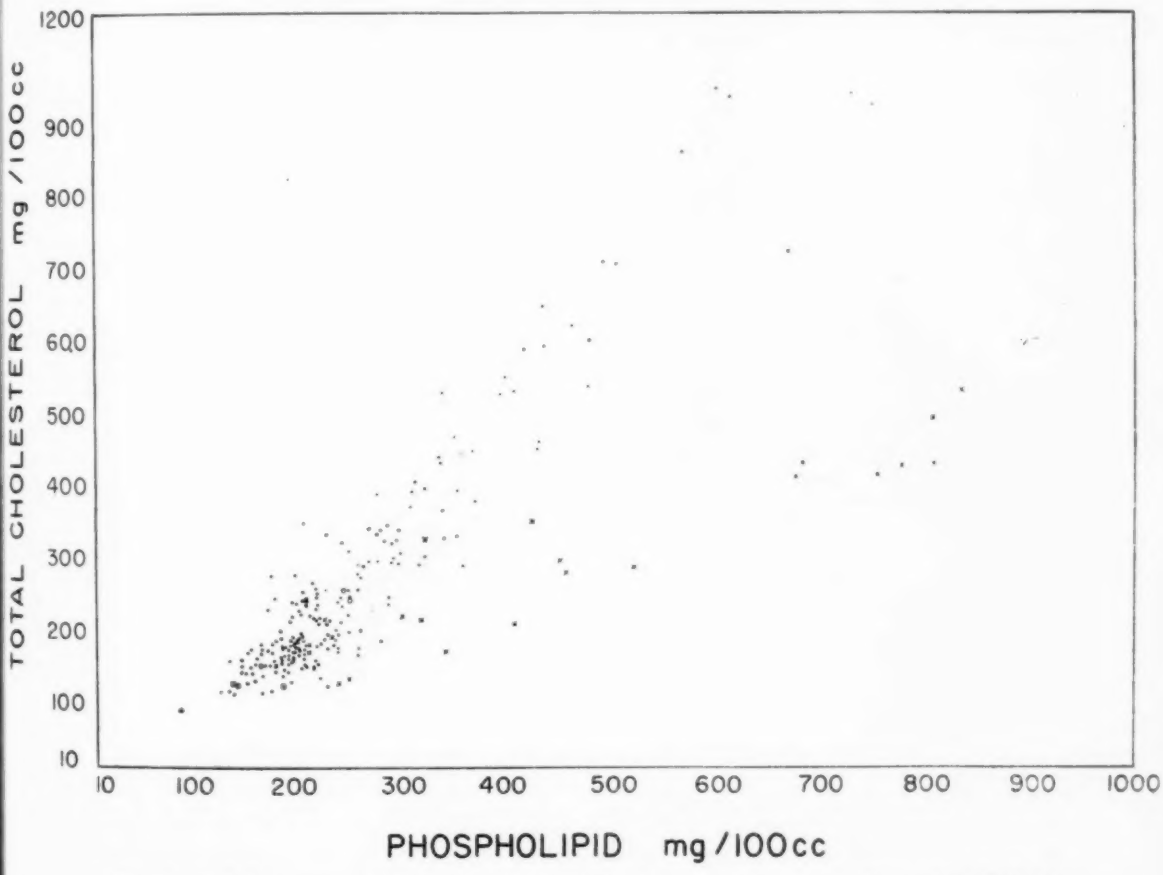


FIG. 1. Total plasma cholesterol values plotted against corresponding phospholipid values. (Liver diseases with normal percentage of esterified cholesterol = O; liver diseases with depressed percentage of esterified cholesterol = X; all others = •)

general relationship was evident, which seemed to break down in some instances. These instances were found to be specimens from patients who had some form of liver disease, with depression of the esterified cholesterol. Those patients with liver disease whose esterified cholesterol level was normal (68–74 per cent

of the total cholesterol), regardless of absolute levels, did not show this deviation from the general rule. This observation simply confirmed the previous results of Man, Peters and their colleagues (18) who had also found a relative (apparent) excess of phospholipid in the presence of the cholesterol ester depression due to hepatocellular failure.

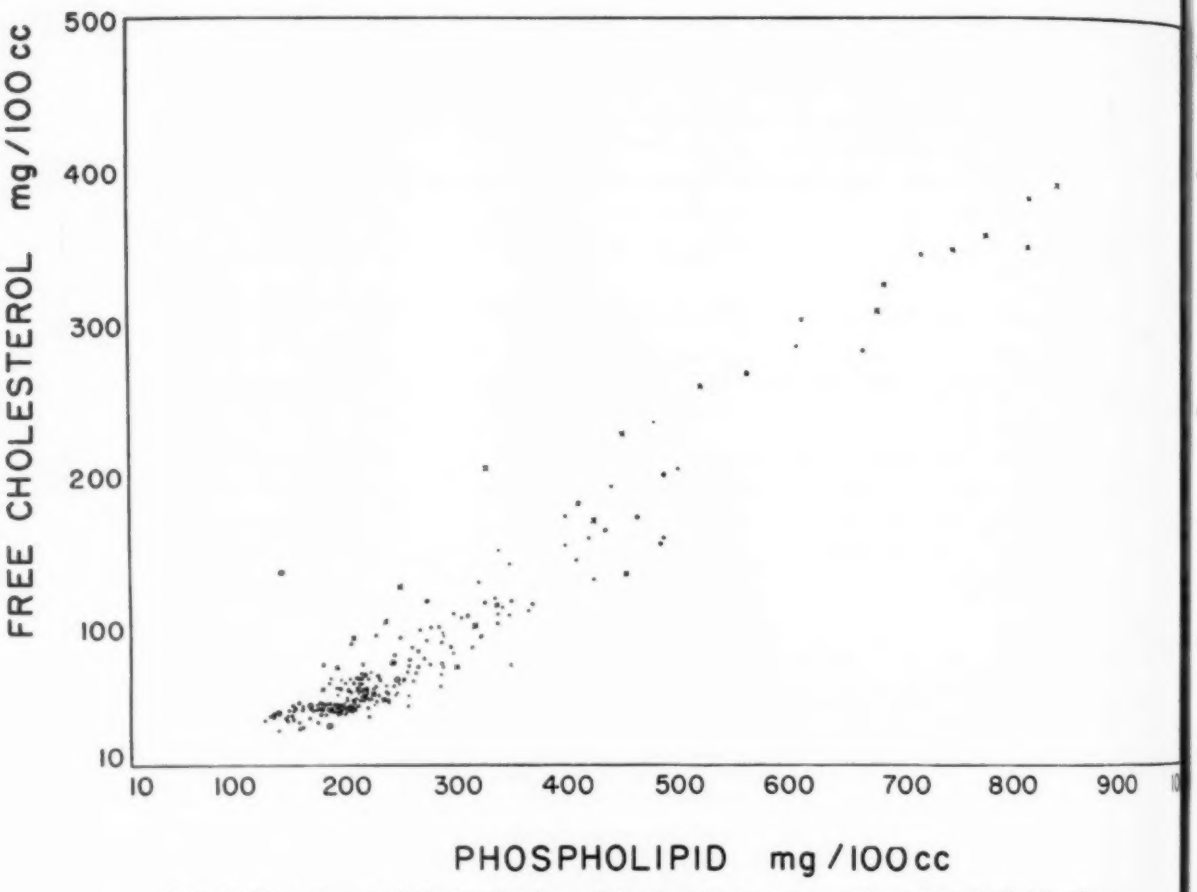


FIG. 2. Free plasma cholesterol values plotted against corresponding phospholipid values. Symbols as in Figure 1.

However, cholesterol does not exist in the blood as a single substance which can be totalled, but in two chemical forms, 1) esterified with fatty acids, and 2) as free cholesterol. Therefore, it seemed more reasonable to compare two substances that actually exist in the blood, rather than one real (phospholipid) and one imaginary substance (total cholesterol). Furthermore, if the problem of this "deviant" group is simply re-stated in terms of free cholesterol, it is evident that the group which exhibited an apparent excess of phospholipid also had relatively more free cholesterol than normal. Figure 2 is the result of these considerations, and demonstrates that there is a relationship between phospholipid and free cholesterol which is independent of the disease state. Our preliminary

report of this finding in March 1950 (22) was independently confirmed by Albrink, Man and Peters in July of that year (23). These conclusions were foreshadowed by the report in 1936, of Chanutin and Ludewig (24), who found in rats, following either partial hepatectomy or ligation of the bile ducts, that the free cholesterol varied directly with the lipid phosphorus.

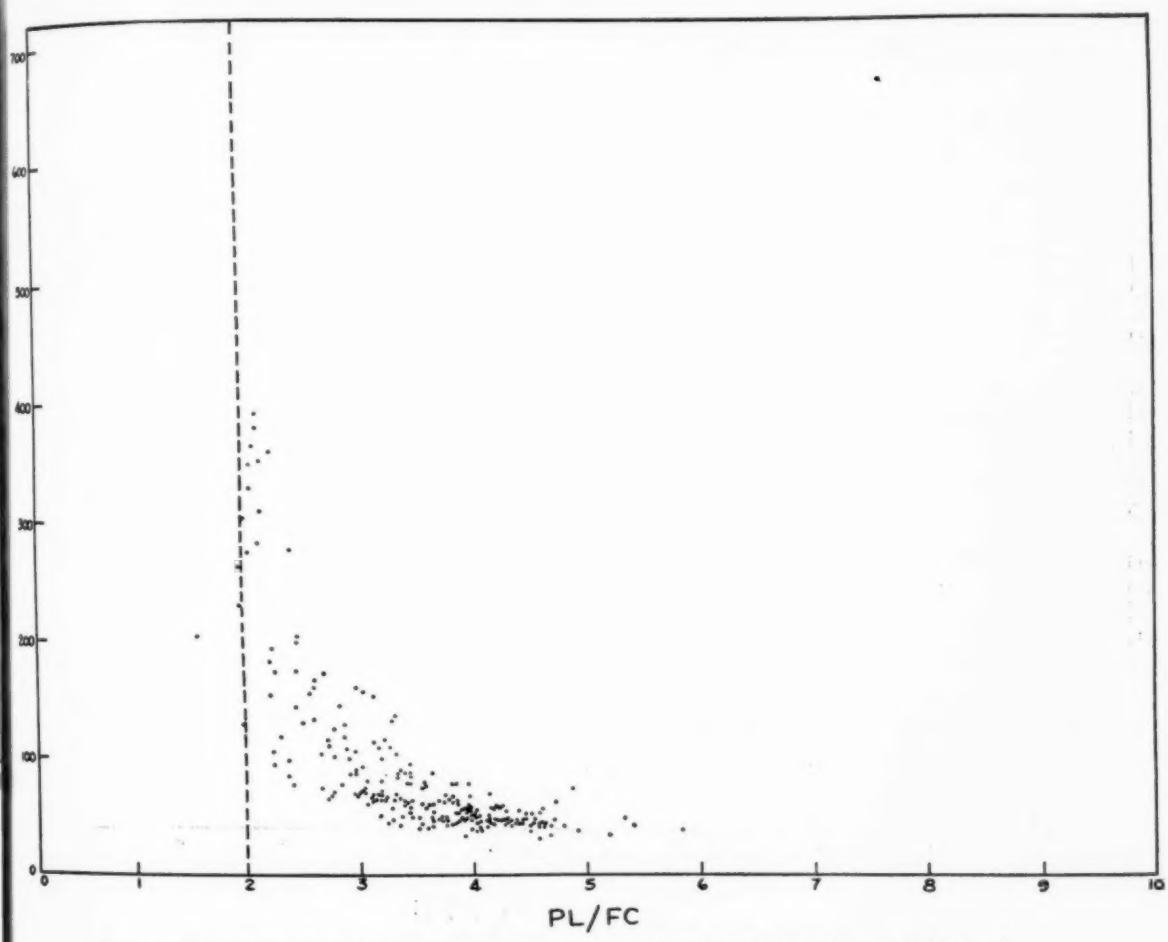


FIG. 3. The effect of the free cholesterol on the ratio phospholipid/free cholesterol.

In Figure 3 we employed a graphic device to learn whether in human hypercholesterolemia, the phospholipids keep pace with the rise in free cholesterol. If so, then the ratio phospholipid/free cholesterol (PL/FC) would remain constant and a straight line paralleling the free cholesterol axis would result. Instead, we see a rapid initial decrease, with a rate which becomes slower as the free cholesterol values continue to rise, until finally the ratio becomes stabilized at a limiting value (PL/FC = 2.00). The one gross exception to this limiting value was a specimen from a woman with severe serum hepatitis, taken shortly before death. This apparent phospholipid deficiency may well be another manifesta-

tion of her overwhelming liver failure. In Figure 4 the data of Albrink, Man and Peters (23) are presented in a similar fashion, demonstrating again that a rising cholesterol level is accompanied by a progressive relative phospholipid deficiency, but only to a point. Further increases in the cholesterol level beyond this point are accompanied by proportionate increases in phospholipid.

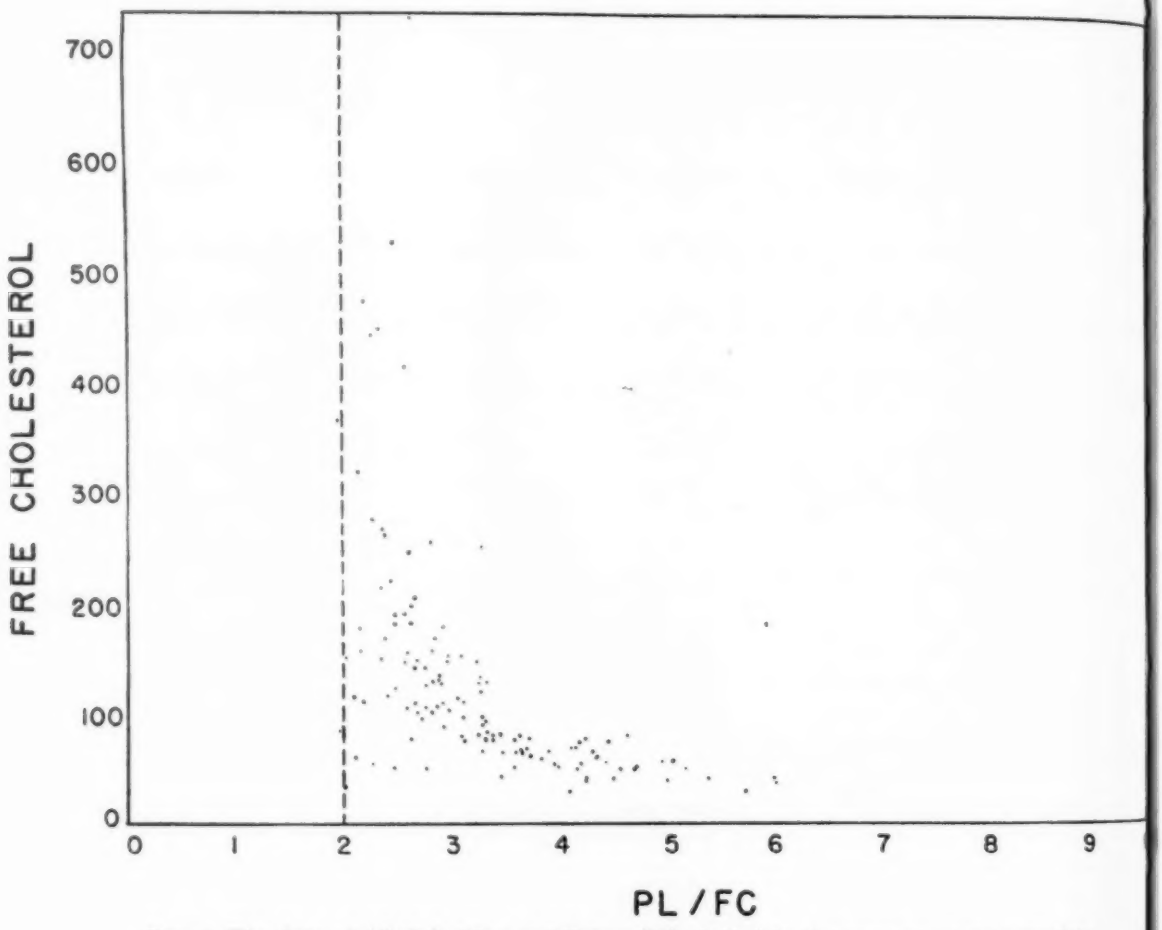


FIG. 4. The data of Albrink, Man and Peters (23) plotted in the same manner as our data in Figure 3.

Since this ratio is expressed as milligrams of phospholipid divided by milligrams of free cholesterol, it would be of interest to learn what the limiting ratio (PL/FC = 2.00) means when translated into molar quantities. This can be done quite simply if one makes the assumption that each molecule of phospholipid contains 1 atom of phosphorus. It is a reasonable assumption, since lecithin and cephalin, both of which contain 1 atom of phosphorus per molecule, make up the majority of the phospholipids of serum; and since the increase in phospholipids in high-phospholipid sera is mainly in the lecithin fraction (7). The calculation is as follows:

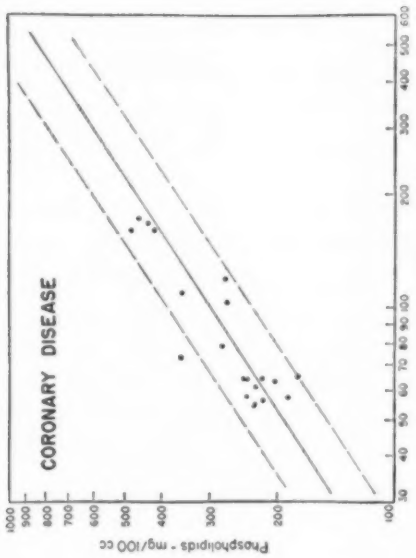
$$\frac{PL}{\frac{25 \times 3098}{\frac{CF}{38664}}} = \frac{PL}{FC} \times \frac{1}{2}$$

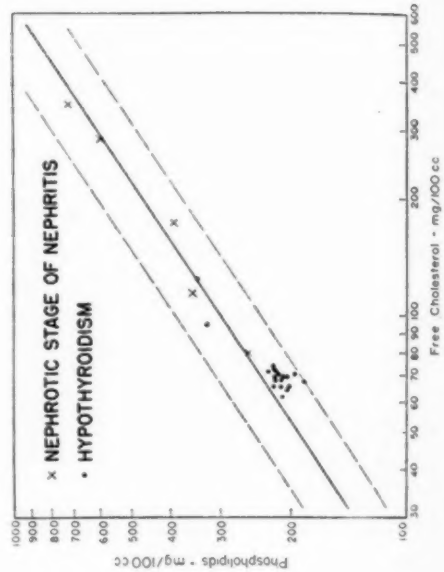
Any of the PL/FC values can be converted into molar values by dividing by 2. Our limiting value of 2, when divided by 2, would suggest that the human organism will not tolerate less than 1 molecule of phospholipid in the plasma for each molecule of free cholesterol.

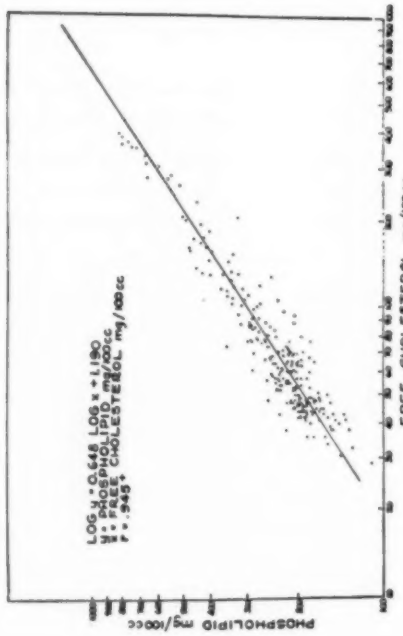
The concept of the phospholipid-total cholesterol ratio as an index of atherogenesis runs headlong into trouble when considered in the light of Figures 2 and 3. In Figure 2 we note that the relationship between phospholipid and free cholesterol is such that, given the value for either one, the other can be predicted within narrow limits. Furthermore, it has been well established that, in health and in all disease states except severe liver failure, there is a constant relationship between free cholesterol and total cholesterol, such that FC = 29% ± 3% TC. Thus, in all other instances, one can derive the probable values of free cholesterol and of phospholipid from the total cholesterol alone. It is difficult to see how any ratio which can be derived from just the total cholesterol level can mean something which the total cholesterol value cannot. We have known for a long time that the total cholesterol level is a poor criterion in the individual case if one wishes to predict the development of, or identify the presence of, atheromatous vascular disease. Keyes (25) has recently shown just how unreliable it is.

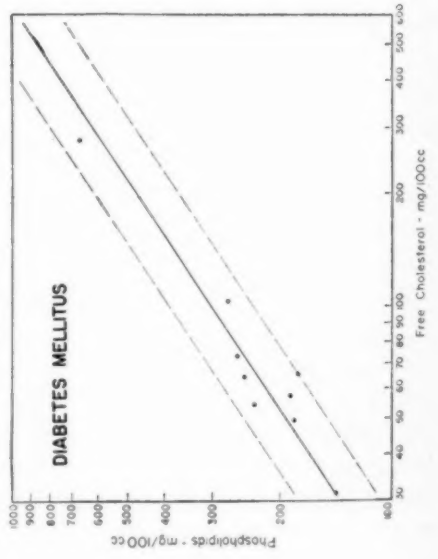
A variety of disease states, considered important in the atherosclerosis problem, have been reported to exhibit phospholipid-total cholesterol ratios which are lower than normal. Some of these states (nephrosis, hypothyroidism, essential xanthomatosis) appear to predispose to atherosclerosis (9); others (myocardial infarction) result from it (11, 12). These diseases have another characteristic in common—a hypercholesterolemia, which may be consistent, or present only in some of the cases. In either instance, the average total cholesterol level of a representative series of cases is elevated when compared with the average total cholesterol level of a normal group.

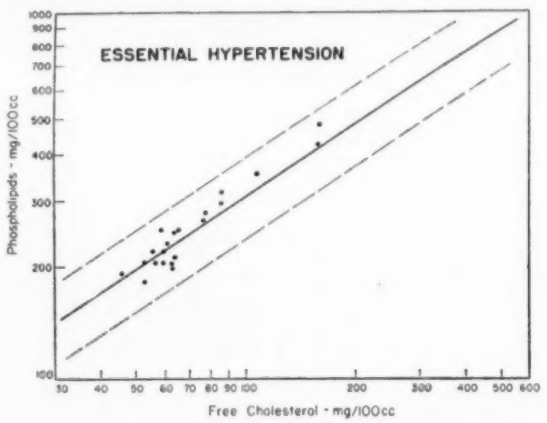
Since none of the diseases implicated in the atherosclerosis problem is characterized by marked liver dysfunction, the free cholesterol value constitutes a constant percentage of the total. Therefore the phospholipid-total cholesterol ratio will bear a constant relationship to the phospholipid-free cholesterol ratio. This allows us to use the curve of Figure 3 to test the effect of hypercholesterolemia per se on the phospholipid-total cholesterol ratio. As noted previously, the higher the free cholesterol value, the lower the ratio (until, of course, the limiting value is approached). Therefore, a group of individuals whose average total cholesterol level is above normal, will inevitably have a lower average phospholipid-total cholesterol ratio, so long as severe liver disease is not present. The average hypercholesterolemia in the diseases mentioned is sufficient in itself


CORONARY DISEASE
Phospholipids - mg/100 cc
Free Cholesterol - mg/100 cc


× NEPHROTIC STAGE OF NEPHRITIS
• HYPOTHYROIDISM
Phospholipids - mg/100 cc
Free Cholesterol - mg/100 cc


LOG y = 0.648 LOG x + 1.190
y = PHOSPHOLIPID mg/100cc
x = FREE CHOLESTEROL mg/100cc
r = .945
PHOSPHOLIPID mg/100cc
FREE CHOLESTEROL mg/100cc


DIABETES MELLITUS
Phospholipids - mg/100 cc
Free Cholesterol - mg/100cc



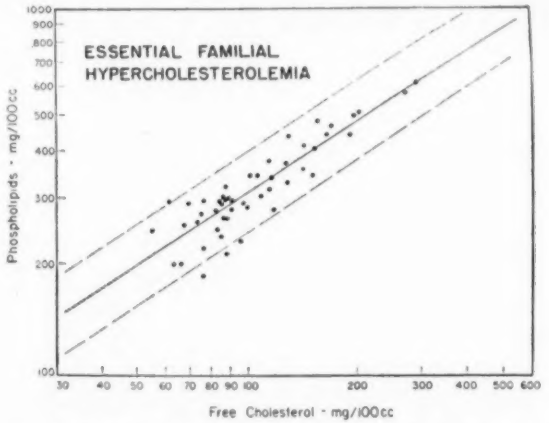
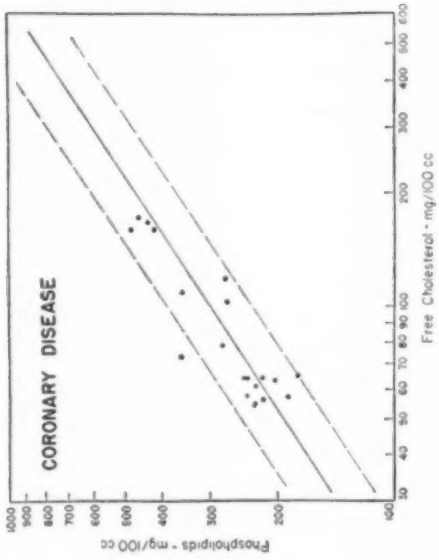
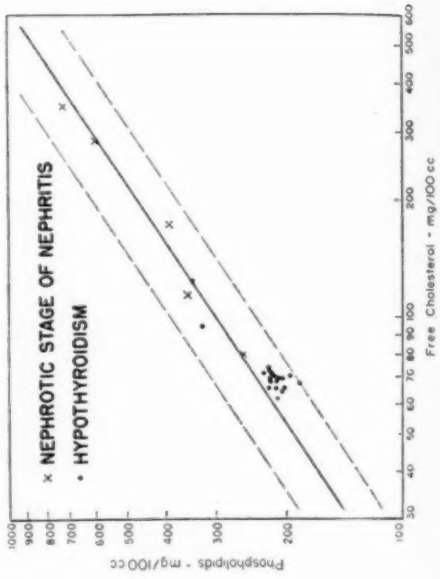
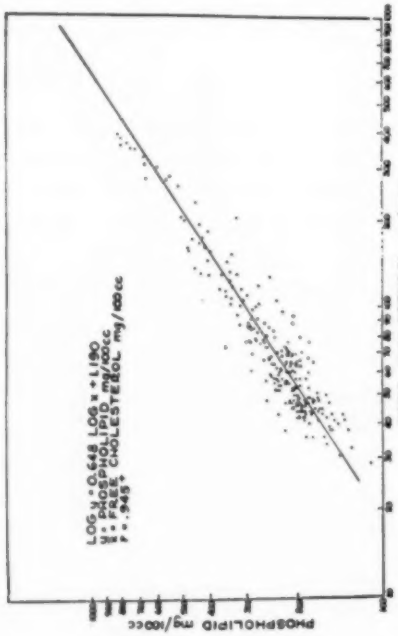


FIG. 5. The relationship between plasma phospholipid and cholesterol values in the entire series, and in several diseases related to the problem of atherosclerosis.


CORONARY DISEASE
Phospholipids - mg/100 cc
Free Cholesterol - mg/100 cc


× NEPHROTIC STAGE OF NEPHRITIS
• HYPOTHYROIDISM
Phospholipids - mg/100 cc
Free Cholesterol - mg/100 cc


LOG Y = 0.648 LOG X + 1.190
Y = PHOSPHOLIPID mg/100cc
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r = .945
PHOSPHOLIPID mg/100cc
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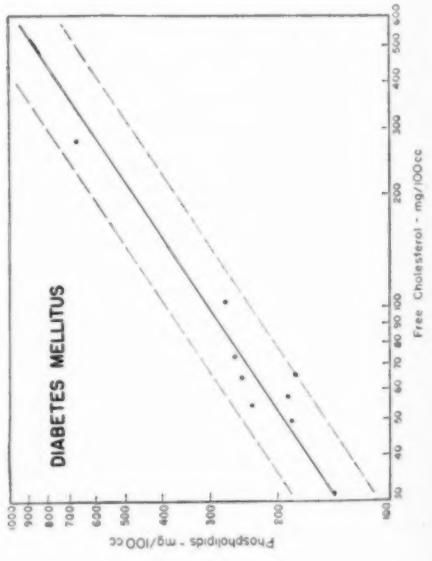
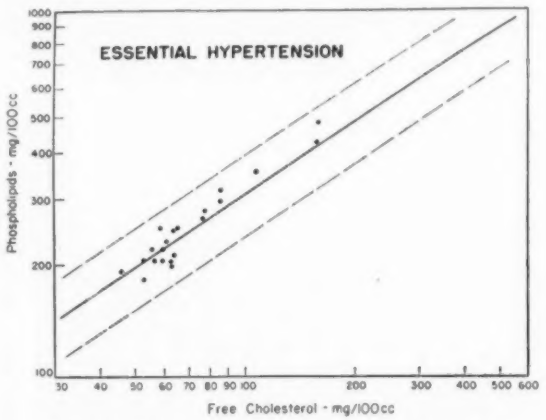

DIABETES MELLITUS
Phospholipids - mg/100 cc
Free Cholesterol - mg/100cc



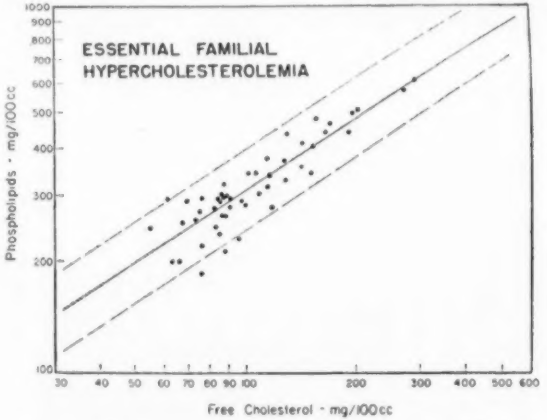


FIG. 5. The relationship between plasma phospholipid and cholesterol values in the entire series, and in several diseases related to the problem of atherosclerosis.

to explain the lower (group average) phospholipid-cholesterol ratios which have been reported.

This explanation for the low ratios in these diseases has advantages other than directness and simplicity; it avoids the necessity for trying to relate their low ratios to their other common denominator, atherosclerosis. So long as normocholesterolemic patients (with, of course, normal ratios) continue to die from coronary atherosclerosis—a distressingly common experience—whereas some familial hypercholesterolemics (26) live out a normal life span in spite of their low ratios, the latter approach will require much ingenuity to defend. In fairness to the investigators who have advanced this concept, one must concede that none of them has claimed that the phospholipid-cholesterol ratio is a "Wassermann" for atherosclerosis. Nevertheless, the cautiousness of their conclusions has not prevented a widespread and growing enthusiasm for this interpretation of their comments. It may be hoped that the alternative explanation of these low ratios advanced here will help temper this uncritical enthusiasm.

It might be objected that we have examined this problem only from the standpoint of a miscellaneous group, and that these "atherogenic" or "athero-subsequent" diseases might be presenting deviations from the general rule which are not great enough to be evident in such a group analysis. This possibility has been investigated by deriving a mathematical expression for the relationship between free cholesterol and phospholipid for the entire group, and then testing individual disease states separately for agreement with this general relationship (27). The results are expressed in Figure 5. The upper left graph demonstrates the entire series. The straight line is derived from the equation calculated from this series; "r" is the correlation coefficient between this straight line and the determinations plotted. In the other graphs of this figure, the straight line representing the over-all group has been drawn, and dotted lines at a distance of ± 2 standard deviations of the logarithm of y (the phospholipid value) are also included. If our contention is correct, that the relationship between free cholesterol and phospholipid is a general one, independent of disease state, then any reasonable sample of the population, no matter how selected, should conform to this rule. If so, then 95 per cent of the determinations should fall within the area bounded by these two dotted lines. This is the case in each of the disease states so tested, as shown in the remaining group of Figure 6.

It should be emphasized that the phospholipids are probably only one factor in the complex mechanism which maintains the normally fine colloidal dispersion of the other more hydrophobic, plasma lipids. Abundant evidence has been brought forth that the serum proteins (28–30) and perhaps heparin (30–32) play a vital role in this process. The place of the phospholipids in this dispersing system is still not clear, but it is now certain that they are not solely responsible. The recent production of clearing of lipemic sera in vitro by biologic systems which do not involve changes in concentration of the lipids (30, 32) would certainly seem to have settled this point. In this connection, it is interesting that the only instance of apparent exhaustion of the dispersing effect of phospholipid encountered by Ahrens and Kunkel (9) was in a patient with a disease which

thus far has not been implicated in the problem of atherosclerosis—idiopathic hyperlipemia.

CONCLUSIONS

1. A biologic relationship is demonstrable between the phospholipid and free cholesterol in plasma, which is independent of disease state.
2. Under conditions in which the free cholesterol forms a constant proportion of the total cholesterol, a relationship can be demonstrated between phospholipid and total cholesterol, but this is a mathematical device and not a biologic relationship.
3. In the absence of severe liver disease, the relationship between free cholesterol, total cholesterol and phospholipid is such that, given the value for any one of these, the values for the others may be predicted within narrow limits.
4. The lower average phospholipid-cholesterol ratios encountered in certain disease states are the result of their average hypercholesterolemia and are not unique to those diseases related to atherosclerosis.

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CARDIAC RESUSCITATION

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The sudden and unheralded cessation of the heart beat of a patient on the operating table can happen in the young as well as in the old. The term cardiac arrest is a relatively new expression to which few of us were introduced during our formal medical education. However, the condition it describes is not new and its connotations are intimately associated with anesthesia. After the successful introduction of ether and chloroform anesthesia in 1846 and 1847, respectively, there soon occurred poorly understood incidents of collapse under anesthesia.

Lane (1) in 1902 was the first surgeon to restore the heart beat after arrest during an operation. In his 65-year old patient the subdiaphragmatic approach was used. There followed a moderate number of scattered reports of successful revival, but unfortunately it appears that the medical profession made little if any concerted effort to prevent or treat these cataclysmic disasters. The main stumbling block in the path of progress seems to have been inability to treat ventricular fibrillation. This is one of the two conditions of arrest that the surgeon encounters in the operating room, and is the more difficult to treat.

In this country, following the turn of the century a considerable amount of knowledge in this field has been contributed by clinicians. The following Clevelanders' names are prominent: Crile, Sollman, Wiggers and Beck. Beck is credited with the practical application of present day resuscitative methods for cardiac arrest in the operating room.

In 1950, through the sponsorship of the Cleveland Heart Society, Beck, Rand and the author instituted a monthly practical course (2) for surgeons and anesthetists. This two-day course deals with the causes and treatment of cardiac arrest, with practical demonstrations in the laboratory. Each participant has an opportunity to bring the laboratory animal's heart out of ventricular fibrillation. The resuscitation procedure is not a complicated one and can be mastered in this short time.

Cardiac stoppage is the enigma and challenge of present day surgery and anesthesia. We cannot turn our backs on such a challenge; we must be ready to meet it. The smug, self-satisfied attitude that this incident will not happen to us is dangerous and unfortunate. Once disaster strikes, the institution and the individual acquire humility forthwith.

Cardiac arrest can happen:

1. In any hospital.

2. To those without known heart impairment almost as frequently as to those with known heart disease.

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3. During operation by the experienced surgeon as well as by the beginning intern.

4. During a long complicated operative procedure as well as during a short simple one.

5. Under local anesthesia as well as under general anesthesia.

6. To persons of any age.

Obviously the best treatment for this condition is prevention. Planning for such an eventuality is one of the best ways to prevent it. An exact pattern must be followed to insure success. The planning must be on an individual plane as well as on an institutional plane, if best results are to be obtained. Preparation will save lives and time-consuming indecisions.

It is my considered opinion that this catastrophe is occurring more frequently than in the past. The figures on the incidence of cardiac arrest, both present and past, are entirely unreliable. Some data often used indicate that it will occur on the average five times each year in every 700-bed active hospital. Anesthetists have made the statement that it will occur once in every 1,000 anesthesias. From consideration of either of these statements as a relative incidence it is obvious that cardiac arrest is not a rarity.

It is estimated that explosions in the operating room take place on the average of about eight times each year in the United States. Compare this figure with the previous ones for cardiac arrest. Next compare the safeguards and preventive measures taken for each type of operating-room disaster. It becomes quite evident that there has been a general lack of preventive measures and of treatment for cardiac arrest during the past fifty years. At times the resuscitation of a patient undergoing impending death under anesthesia is so simple that one must speculate that many lives have been sacrificed which might have been saved.

Time and space do not permit going into the many causes of this condition. At times the cause may be clear-cut; at other times it seems as if the breaking of a link in a chain of circumstances precipitates the disaster. Basically, the greatest hazard to the surgeon in the operating room is anoxia. Important general factors demanding attention are the use of pre-anesthetic drugs, choice of anesthesia, patency of the airway, position of the patient, blood volume, reflexes, and the avoidance of errors of judgment and apathy.

Once the catastrophe has occurred there is no time to improvise methods of treatment. In the confusion it is difficult to think clearly. One of the best methods to insure success is to have a preconceived exact plan of action so well impressed in one's mind that the steps can be carried out almost reflexly. Any correct steps which may be carried out reflexly will result in action without error.

It is just as important to know what *not to do* as what *to do* in this emergency. Time cannot be consumed performing incorrect and unimportant procedures, as there is a time limit of three to five minutes after which the brain is irreversibly damaged from lack of oxygen.

The basic problem is to keep the brain viable and we must focus our attention on this fact and not upon the secondary problem of restoring the heart beat.

Recognition that there are two separate and distinct steps in cardiac resuscitation is important and has frequently been overlooked. The two components are: 1) re-establishment of the oxygen system (first part), and 2) restoration of the heart beat (second part). One should not be confused with the other. After Part 1 has been put in operation, it must be continued until Part 2 is successfully concluded.

In the re-establishment of the oxygen system, oxygen must be delivered into the lungs. Next, there must be enough hemoglobin available to transport it. Finally, a dynamic pump must circulate the oxygen-laden hemoglobin to the brain to keep it alive. The heart remains a satisfactory hydrodynamic pump, provided the surgeon places his hand upon it and squeezes it rhythmically and effectively.

The re-establishment of the oxygen system is the emergency act. An alert anesthetist must get an intratracheal tube in place and deliver 100 per cent oxygen into the lungs. Once the anesthetist can adequately aerate the lungs, the surgeon grasps a knife and boldly slits open the left chest in the fourth or fifth interspace, from the sternum to the underlying bed sheet. Matters such as asepsis and gloves are subordinate and hardly need comment. There is no bleeding because there is no blood pressure. A bleeding incision would indicate that cardiac arrest had not taken place.

The hand is then thrust into the chest behind the heart and pericardium and the heart is squeezed upwards against the sternum. The crisis is now over. The brain can be kept viable.

If the heart does not resume its normal beat at this time, an assistant places a large rib retractor in the wound and a few moments later the pericardium is opened and cardiac massage is immediately resumed. The surgeon must remember that, upon cessation of manual massage, the blood pressure falls to zero.

The operator must decide upon the best method to massage the heart. One method has already been mentioned. Other methods depend upon the relative size of the heart and the surgeon's hand. It may be squeezed with one hand or with two hands. The novice seems to produce a more effective circulation by using the Beck-Rand (3) suction-cup electrodes.

Regardless of the method used, a blood pressure can be maintained which will sustain life for at least eight hours, as in the case of a certain patient who has now returned to a normal life[1].

Up to this juncture it is not known whether the heart is in a condition of standstill or of ventricular fibrillation. Massage is momentarily stopped and the heart observed. Ordinarily the two conditions can readily be distinguished. Cardiac asystole is found more frequently than ventricular fibrillation. The heart in asystole may start after hand massage alone. If it should not resume its beat after adequate massage, drugs should then be used. In this condition 4 to 5 cc. of 1:10,000 epinephrine solution is injected into the chamber of the right ventricle and massage continued.

[1] Personal communication from M. N. Foote of Brooklyn, N. Y.

A heart during ventricular fibrillation is in a state of convulsion. There is a purposeless movement of the heart muscle. This is the more difficult of the two conditions of heart arrest to treat successfully. Very rarely has it been possible to bring the human heart out of this incompatible rhythm without the aid of a defibrillating machine (4). We prefer the fool-proof Beck-Rand (3) machine, with suction-cup electrodes. Every hospital should have one readily available.

To treat ventricular fibrillation successfully, manual massage is carried out, as in the previously mentioned condition, until the myocardium turns from a cyanotic hue to a pink color. At this moment the electrodes are snugly applied and an assistant pushes the button which will deliver a current of 60 cycles, 110 voltage, of 1.5 to 2.5 amperes for one full second into the mass of ventricular muscle. Frequently a weak normal beat will supervene and one must then administer assisted cardiac massage.

In the difficult case in which a normal rhythm does not resume after several shocks, drugs may be of value. In this instance about 3 to 5 cc. of 1 per cent procaine is injected into the chamber of the right ventricle and the previous procedure repeated. Occasionally 1 to 2 cc. of 1:10,000 solution of epinephrine is efficacious, even in the face of ventricular fibrillation.

Do not rely on drugs. They should be used as a last resort. Do not clutter up your brain or the operating table with the many kinds of cardiac drugs. There are two dependable drugs which should be available for this emergency—epinephrine and procaine. Your consultant may use the many others during the postoperative management.

The major causes for failure to restore the normal heart beat are: 1) poor aeration of the lungs, 2) ineffectual manual massage, 3) retention of carbon dioxide, and 4) intrinsic heart disease.

In the successful case the surgeon should not be in a hurry to close the chest. The patient should be kept on the surgical floor for some time. He should *not* be returned immediately to his room.

Several types of results may be obtained.

1. Full recovery of cerebral function, respiration, and heart beat. This is the ideal result and the one that is hoped for.

2. Full recovery of respiration and heart beat with delayed recovery of cerebral function, but eventual complete recovery. These patients may have a clouded sensorium for a short time or for several days. Convulsions may continue for several days also. Mollison (5) reported a patient who remained unconcious for seven days and showed signs of cerebral irritation for a period of fourteen days. Permanent recovery ultimately occurred.

3. Full recovery of respiration and heart beat, but permanent impairment of cerebral function. Fortunately this result does not occur frequently. The majority of these people either recover completely or expire.

4. Full recovery of heart beat and blood pressure, but delay in recovery of normal respiration. Bohn (6) reported a case in which the normal respiratory function was not obtained until two and one half hours following the return of a cardiac rhythm.

5. Temporary recovery of heart beat, but gradual decrease of blood pressure and death within two to twelve hours, in spite of all measures to sustain blood pressure.

6. Full recovery of respiration and heart beat, but death from cerebral edema on the following day or succeeding days.

7. Recovery of heart beat without recovery of respiration; the heart continues to beat only as long as mechanical respiration is administered.

8. Inability to restore heart beat. This is usually due to poor oxygenation or inherent cardiac disease. (In such unsuccessful cases, it is a good policy to have the anesthetist and a hospital representative accompany the surgeon at the time the family is informed of this misfortune.)

The *secret* for success is good oxygenation and the application of a preconceived exact pattern of procedure. At the onset of this emergency, time cannot be wasted on consultation, vacillation or indecision.

The results are in inverse ratio to the length of time elapsing from cardiac arrest to the re-establishment of the oxygen system. For success in the majority of cases, courage, speed, clear thinking, perseverance and a few special instruments are all that is necessary.

SUMMARY

The requirements for success in the treatment of cardiac arrest during surgery are discussed. The importance of separating the procedure into two separate components is stressed. The only drugs necessary during this emergency are epinephrine and procaine. A sterile emergency kit and a defibrillating machine should be available at all times in the operating room. Planning for such a disaster is one of the best methods of preventing it.

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NEPHRITIS IN OLD AGE

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In mortality tables of older individuals, the diseases labelled "degenerative" are important. Included in this group are those disorders termed nephritis. The term nephritis includes a number of diseases of the kidneys characterized by bilateral nonsuppurative lesions associated with a variable degree of proteinuria and casts. In old age any of the generally occurring nephritides may appear, but those of importance are few in number. This discussion will include those of importance because of their profound effect. They are:

1. Arteriosclerosis of the kidney.
2. Nephrosclerosis.
3. Chronic pyelonephritis.
4. Chronic glomerular nephritis.
5. Intercapillary glomerulonephrosis.

Arteriosclerosis of the kidney. This term requires some comment. One might assume that by this condition is meant the normal aging process in the vascular tree, as it affects the kidney. Whether this is true, in essence, depends upon one's outlook on arteriosclerosis and its etiology. How much of arteriosclerosis is purely normal aging and how much, particularly of the atherosclerotic type, is not normal aging, is a problem under a great deal of discussion and dispute. The pros and cons will not be considered here. Suffice it to say that involvement of the arteries with the sclerotic process leads to impairment of circulation. In the kidneys this at times leads to obstruction and infarction, which is characterized by pain and bloody urine. Such changes involve areas of one kidney only and do not lead to renal insufficiency unless other damage is present.

Studies which have been carried out on elderly individuals who are presumably normal by usual clinical standards indicate that the aging process produces a progressive dimunition in functions of the kidney. Detailed observations with clearance methods show impairment of blood flow through the kidneys. Landowne and Shock's report (1) indicates that there is a decrease in renal blood flow in people over 50 years of age. With no reduction in blood pressure and a cardiac output that is essentially unchanged, this denotes an increase in resistance in the renal vascular system which may be even greater than the overall increase in resistance in the circulation generally. Olbrich and his co-workers (2), by means of clearance studies, showed that the aged have a diminished blood supply to the kidneys, resulting in quantitative changes in renal function. They found that the glomeruli filtered the plasma with efficiency, yet inulin clearance was depressed because of reduced renal plasma flow associated with vascular changes. Their subjects with high systolic and low diastolic pressures had a reduction in effective renal plasma flow. Tubular excretory capacity was dimin-

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ished, and urea clearance was reduced about 25 per cent. This impairment affects the concentrating ability of the kidneys and in turn produces larger volumes of dilute urine. Such patients commonly show frequency of urination and nocturia, but little else. Why then are these changes important clinically? Renal insufficiency seldom develops from these changes alone. However, renal reserve is reduced and there are grave consequences when there is a suddenly impaired fluid intake, such as occurs in infections, shock-like conditions, and cerebral accidents. Uremic states are likely to develop under these circumstances. The following is a typical example:

A white female, aged 72, had recently complained of rectal hemorrhage. The history indicated that about forty years previously rectal surgery had been performed, and a stricture resulted. Since that time the stools had been of small caliber. Following an upper respiratory infection she had recently taken a cathartic and had passed considerable red blood with the ensuing action. Physical examination at the time disclosed a blood pressure of 160/90. Moderate retinal sclerosis was present and the peripheral vessels were moderately thickened. The lungs were clear and the heart was normal. The examining finger could not be inserted into the rectum. A chest roentgenogram and an electrocardiogram revealed nothing abnormal. Blood urea nitrogen concentration was 16 mg. per 100 cc. The urine had a specific gravity of 1.015, contained no albumen or sugar, and microscopically showed an occasional granular cast.

Rectal dilation under gas anesthesia resulted in the breaking up of several adhesive bands. There was considerable bleeding for several days. Nausea developed and intravenous fluids were given. Repetition of the BUN showed an elevation to 36 mg. per 100 cc. Review of the fluid intake showed an average of 2,200 cc. taken daily. The specific gravity of the urine did not rise above 1.015. These findings indicated inadequate fluid intake. Nausea and vomiting persisted until adequate fluids (3,500 cc.) were given daily. This permitted 1,000 to 1,200 cc. for loss by skin and lungs and an adequate urine volume (2,000 to 2,200 cc. daily) for output of nitrogen and other waste products. Recovery ensued.

Here is an example of a patient who, through the aging process, had lost much of her renal reserve. When unable to excrete nitrogen and other wastes in 1,000 cc. of urine daily, nitrogen retention (and its symptoms) developed. A younger patient with adequate kidney reserve and ability to concentrate urine to a specific gravity of 1.028 would have had no nitrogen retention with 800 cc. of urine daily; but in this elderly patient the disturbed fluid intake was sufficient to bring a relatively asymptomatic renal state to the clinical horizon and make it very important.

Similarly, in cerebral accidents or in shock-like states, renal impairment of this type suddenly becomes clinically important. Previously, judged by simple examination without stress tests, it may have been unrecognized or did not seem important.

Nephrosclerosis. This term is used to indicate the renal damage accompanying diastolic hypertension. Even when the diastolic hypertension is of a mild type it exerts an effect on renal function above and beyond that of renal arteriosclerosis alone. Comparison of groups with and without diastolic hypertension shows this increment in damage very conclusively.

The problems of nephrosclerosis, both benign and malignant, in older patients

are those of the hypertensive kidney in earlier age groups. No more need be said here regarding this subject.

Chronic pyelonephritis. Chronic pyelonephritis will be mentioned only briefly. The problem relates to impaired renal function as the result of infection, obstruction, or both. Obstructive phenomena may be "physiologic," such as seen in cord bladder, or they may be due to true anatomic obstruction as occurs in benign prostatic hypertrophy. Although there may be difficulty at times in distinguishing pyelonephritis from other types of renal damage, generally the relationship of local infection and obstruction and the asymmetry of the lesion indicate the diagnosis.

Chronic glomerular nephritis. The problems of glomerular nephritis do not differ much from those in younger age groups. Since age adds little to the problem, nothing further will be said about this type of lesion.

Intercapillary glomerulosclerosis. The recognition by Kimmelstiel and Wilson in 1936 (3) of a distinctive hyalinization of the intercapillary region of the glomerular tuft in certain diabetics paved the way for the establishment of this renal state as an entity apart from glomerular nephritis and nephrosclerosis. Although such lesions have been found in diabetics from the ages of 18 to 78 (4), the clinical state has been found most frequently in older patients. Twice as common in women as men, intercapillary glomerulosclerosis at the clinical level appears in diabetics of long standing, often with mild diabetes. In some reports (4) the average age is 60 years. The condition is, therefore, one of the important medical renal states of old age.

Clinically the syndrome is characterized by hypertension, albuminuria and retinopathy. Edema is inconstant. Although hypertension is not an essential part of the picture, the complications are frequently those of vascular damage, arteriosclerosis obliterans, neuropathy and congestive heart failure. Death is commonly from a cerebrovascular accident or uremia. With frequently associated hypertension, the retinopathy is often characterized by the presence of the cottonwool exudates and flame-shaped hemorrhages of hypertension. Characteristic, however, are the hard, sharply demarcated exudates, and persistent punctate hemorrhages of the type described in diabetic retinitis. Damage to veins and a proliferating retinopathy sometimes occur as well. Edema is usually described as that accompanying excessive protein loss through the kidneys, with associated hypoalbuminemia. In the group studied by Henderson and his associates (4), 47 per cent of the patients showed edema, but in only 4 cases out of 29 was it of the nephrotic type. Some cases were due to congestive heart failure.

The differentiation of intercapillary glomerulosclerosis from glomerular nephritis and nephrosclerosis rests in sharp differences in their course and prognosis. Patients with the diabetic nephropathy generally live much longer after symptomatic renal findings appear. The various tests of kidney function are not very helpful in the differentiation. The pattern of change closely resembles that of chronic glomerular nephritis (5). One must depend upon clinical criteria, which are clear enough in advanced cases, but obscure in early or mild forms of the disease, or in those instances in which hypertension and its effects coexist.

CONCLUSIONS

An attempt has been made to evaluate briefly several of the important renal entities occurring in old age and commonly included under the term *nephritis*. The distinctive changes of old age itself enter into the problem of evaluation and differentiation.

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RESPONSE OF AGED PERSONS TO ADMINISTRATION OF SALT AND DESOXYCORTICOSTERONE ACETATE

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Although the most striking effect of desoxycorticosterone acetate (DCA) is the retention of sodium and the excretion of potassium, under certain conditions it may act to retain both sodium and water (1, 2) (3, lit. reviewed) (4–8), and under other conditions to further the excretion of water (3, 9) even to the point of the production of a diabetes-insipidus-like picture (3, 11–18). Soffer and his associates (19) made these phenomena the basis of a test for Cushing's syndrome, believing that in that condition the normal sodium-retaining effect of desoxycorticosterone acetate was lost.

Inasmuch as wide fluctuations in the values for urinary volume, sodium and chloride have been observed in the performance of such tests, we have attempted to analyze statistically the data obtained in our own laboratories, in relation to age; and whenever possible, to correlate these with the eosinophil counts and electrolyte excretions following the administration of adrenocorticotropin (ACTH).

PROCEDURE

All tests were carried out in accordance with the procedure of Soffer and his associates (19). Food was withheld from 7:00 p.m. on the evening preceding the study, until the completion of the tests. No fluid was given during the same period except as specifically stated. At 6:00 a. m. on the morning of the studies, each subject voided and discarded the urine. The subject then drank 500 cubic centimeters of water, and all urine voided in the three-hour period from 6:00 to 9:00 a.m. was labelled as Period I and saved. At 9:00 a.m., 10 grams of sodium chloride (representing approximately 171 milliequivalents of sodium) were administered intravenously as a 5 per cent aqueous solution. The speed of the injection was timed to complete the infusion within the half hour. All of the urine voided between 9:00 a.m. and 12:00 noon was collected, pooled, and labelled Period II. Three days later, the procedure was repeated in each subject, except that at 10:00 p.m. on the preceding evening 10 mg. of DCA was injected intramuscularly. Thus, in each subject, four specimens of urine were collected for examination, representing conditions as follows: *Period I*—before the administration of DCA and salt; *Period II*—before the use of DCA but after salt; *Period III*—after DCA but before the giving of salt; and *Period IV*—after DCA and salt. The urinary volume of each period was recorded and quantitative determinations were made on each of the four specimens for sodium, potassium,

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chloride, 17-ketosteroids, uric acid and creatinine. Sodium and potassium were determined by the technic of Overman and Davis (20), and chlorides according to the method of Wilson and Ball (21).

More than 200 tests were carried out on 130 individuals. Of these tests, 71 were performed on 50 subjects who were free of renal disease and whose endocrine status was believed to be such as not to interfere with the results. They were divided into three groups: 1) those above 65 years of age—14 patients, representing 22 tests; 2) those between 50 and 64 years—16 patients, representing 19 tests; and 3) those under 50 years—20 patients, representing 30 tests.

The behaviors of these three groups under the conditions imposed by the test have been compared in regard to the effects of age upon (a) urinary volume, (b) the excretion of uric acid, creatinine and 17-ketosteroids, (c) the excretion of administered salt, and (d) the influence of desoxycorticosterone upon the excre-

TABLE 1

Age group (yrs.)		Group 1, over 65 (14 subjects)				Group 2, 50–64 (16 subjects)				Group 3, 17–49 (20 subjects)			
Period*		I B.S.**	II A.S.†	III B.S.	IV A.S.	I B.S.	II A.S.	III B.S.	IV A.S.	I B.S.	II A.S.	III B.S.	IV A.S.
Urine													
Volume (cc.)		301	332	180	263	364	249	299	259	467	310	354	244
17-Ketosteroids (mg.)		1.23	1.21	1.48	1.18	1.25	1.12	1.24	1.28	2.37	2.54	2.62	2.40
Uric acid (Gm.)		.07	.07	.07	.09	.08	.07	.05	.07	.09	.09	.07	.08
Creatinine (Gm.)		.14	.16	.14	.14	.14	.14	.14	.13	.27	.25	.27	.20
Sodium	mEq.	18.0	42.4	12.8	37.2	18.3	35.9	13.2	31.9	16.4	48.5	7.7	29.4
Chloride	mEq.	18.7	45.1	16.0	41.7	19.8	37.2	19.2	39.0	18.8	51.1	10.4	32.5
Potassium	mEq.	9.3	15.0	13.1	13.4	10.2	16.2	10.2	13.6	10.1	16.5	8.3	16.3

* Period I—Before DCA and before salt.**
Period II—Before DCA but after salt.†
Period III—After DCA but before salt.
Period IV—After DCA and after salt.

tion of sodium and chloride before and after the administration of 10 grams of sodium chloride.

RESULTS

The averaged data for the four experimental periods, arranged in relation to age, are contained in Table 1 and are considered serially.

A. *Urinary volume.* It will be observed that the average urinary volume after the administration of DCA (Periods III and IV, respectively) was lower than in the corresponding periods prior to its use (Periods I and II). When treated statistically, however, these values were of no significance. The administration of salt did not appreciably alter the urinary volume (Periods I and II), except in Group 2 (subjects between 50 and 64 years of age) in whom the values were slightly higher following, than before its administration (Table 1). However, with one exception, none of the variations in urinary volume was significant

when treated statistically. In Group 3 (subjects under 50 years of age) there was a decrease in urinary volume (113 ± 49 cc.) as a result of the administration of DCA in the periods before salt administration (I and III). The corresponding T value was 2.3 and P, 0.04. This decrease in urinary excretion suggests a more ready response of the younger individual to the retention of water in conjunction with the retention of sodium.

B. *The excretion of uric acid, creatinine and 17-ketosteroids* (Table 1). As might be expected, the youngest age group excreted more creatinine and a larger quantity of 17-ketosteroids than the older individuals, but neither these values nor those for uric acid were strikingly or significantly altered by the administration of DCA or salt.

C. *The excretion of administered salt* (Table 1). There was considerable variation from subject to subject in the percentage of administered salt excreted.

For the purposes of the test, it is assumed that the increased excretion of salt following the administration of 10 grams of salt (171 milliequivalents expressed as sodium or chloride) is due entirely to the added electrolyte. Therefore by subtracting the amount excreted in Period I from that excreted in Period II, the influence of the added salt should be apparent. On this basis, the average excretions for the subjects in Groups 1, 2 and 3 were 24.4, 17.6 and 32.1 milliequivalents of sodium, respectively, and 26.4, 17.4 and 32.3 milliequivalents of chloride, respectively. Although these differences were considerable, the variations from subject to subject were so marked as to make these variations from group to group of no statistical significance. In other words, under the conditions of the test, age did not materially influence the ability of the subject to remove added salt from the system by way of the kidney.

D. *The influence of DCA upon the excretion of sodium, chloride and potassium before and after the administration of sodium chloride.* Our data under this heading for the three age groups are best considered, first by comparing the urinary excretion of sodium, chloride and potassium following the ingestion of 500 cc. of water before and after the administration of DCA (Periods I and III, Table 1) and, secondly, by analyzing the influence of infused salt upon such excretion (Periods II and IV, Table 1).

The urinary excretion of sodium, chloride and potassium following a 10-milligram dose of DCA and the ingestion of 500 cc. of water (Periods I and III)

a. The behavior of sodium (Table 1 and Fig. 1). It is obvious from a glance at Table 1 that DCA caused a retention of sodium in all three groups of subjects and that this action appeared to be more noticeable in subjects under 50 years of age than in those who were older. In all instances, these variations within each group were highly significant statistically. However, except in Group 3, the administration of salt in the amount used, materially depressed this action.

In Figure 1 are depicted the values for sodium, before and after DCA administration in the periods prior to the giving of salt (Periods I and III). At first glance, it would appear that subjects under 50 years of age showed a much more marked capacity for retaining sodium than did those who were older.

However, when treated statistically, the standard deviation for the difference between Groups 1 and 2 was 3.5 ± 2.4 milliequivalents, with a T value of 1.5 and a P of 0.15. The corresponding comparison between Groups 2 and 3 yielded a standard deviation of 3.6 ± 2.6, with a T of 1.4 and a P of 0.18. Therefore, although these facts seem to show a trend towards a greater retention of sodium by younger people subjected to the influence of DCA, such differences are not statistically significant, and we doubt that they would become so in a larger group of individuals subjected to the same conditions as were used in the present tests. The excretion of administered salt was rapidly effected in all three groups of subjects, little, if any, variation with age being apparent.

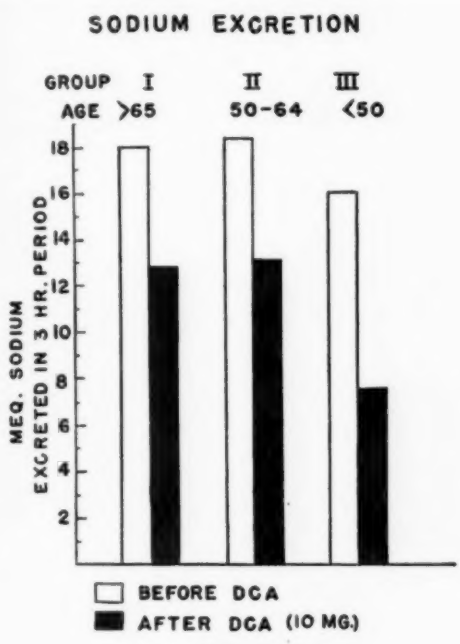

FIGURE 1

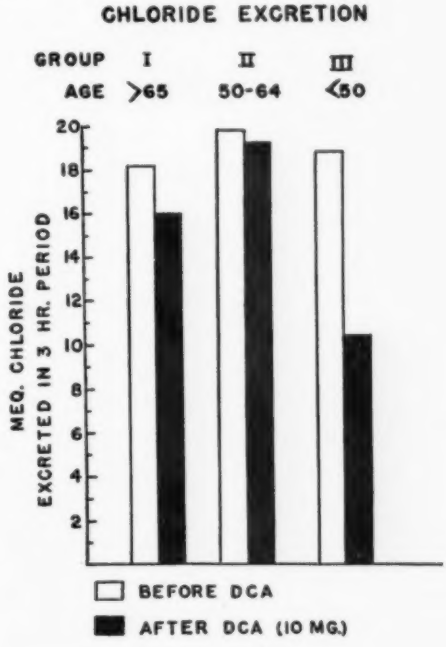

FIGURE 2

b. The behavior of chloride (Table 1 and Fig. 2). The retention of chloride as a result of the administration of DCA was not so marked as the retention of sodium. In the three age groups, this retention of chloride per subject averaged 2.7, 0.6 and 8.4 milliequivalents for Groups 1, 2 and 3 respectively. In those above 50 years of age (Groups 1 and 2) the amount of chloride retained was small and not statistically significant but in Group 3 the chloride-retaining effect was obvious on inspection and confirmed by statistical evaluation, the average of 8.4 milliequivalents excreted for the three-hour period having a standard deviation of ±2.1.

The differences in the values for chloride between Groups I and II following the administration of DCA were negligible, and between Groups I and III showed a trend which was not statistically significant, the difference being 5.7 ± 3.2 with a T value of 1.8 and a P of 0.07. The corresponding difference between Groups II and III was 7.8 ± 3.9 with a T of 2.0 and a P of 0.05.

From these data it is evident that younger individuals are more susceptible to the sodium and chloride-retaining action of DCA than are older people, and that the influence of this steroid upon sodium is greater than its influence upon chloride.

c. The behavior of potassium (Table 1 and Fig. 3). DCA tended to increase the excretion of potassium but the trend was so slight that the differences

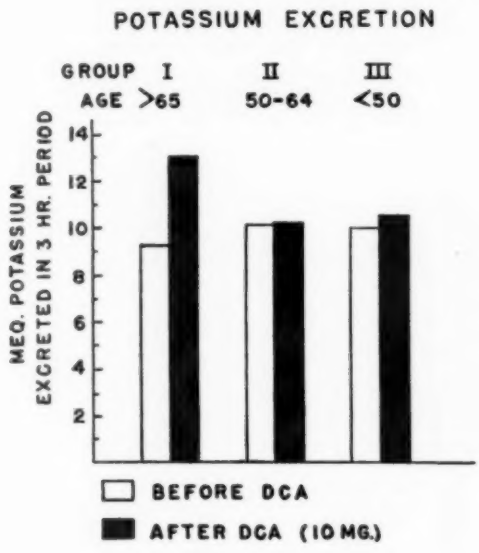

FIGURE 3

TABLE 2

Influence of Added Salt (171 mEq.) upon Sodium and Chloride-Retaining Action of DCA (10 mg.) in Human Beings of Different Ages

Age groups (yrs.)	Excretion (mEq.) during 3 Hours Following Salt					
	Over 65 (Group 1)		Between 50 and 64 (Group 2)		Under 50 (Group 3)	
	Na	Cl	Na	Cl	Na	Cl
Salt alone	24.4	26.4	17.6	17.4	32.1	32.3
Salt plus DCA	24.4	25.7	18.7	19.8	21.7	22.1
*Net difference**	*0.0*	*+0.7*	*−1.1*	*−2.4*	*+10.4*	*+10.2*

* Theoretically, positive balances represent the net effect of DCA. The "net difference" in Group 3 as compared with Groups 1 and 2 is highly significant at the 5 per cent level of confidence.

between the amounts excreted before and following the injection of 10 milligrams of the steroid were negligible in all three groups of subjects (Fig. 3).

The influence of added salt upon the action of DCA in the three age groups (Tables 1 and 2 and Fig. 4).

The data in Table 2 and in Figure 4 were obtained in the following way: The milliequivalents of electrolyte excreted in the fore periods from 6:00 to 9:00 a.m.

were subtracted from the milliequivalents excreted in the period after salt infusion, from 9:00 a.m. to 12:00 noon. Thus, in Table 2, in the line marked "Salt alone," all values represent the difference between the excretions of electrolyte in Periods II and I; and in the line marked "Salt plus DCA," the values represent the difference between the excretions in Periods IV and III. The net differences are shown graphically in Figure 4 and indicate the net retaining or excreting effect of DCA following the subjection of the individual to an appreciable "salt load." In fact, each value in Table 2 indicates the portion of the added salt which was excreted in a three-hour period by the average subject of the age group indicated. It will be noted that this fraction was greatest for those in the group under 50 years of age and least in those between 50 and 64

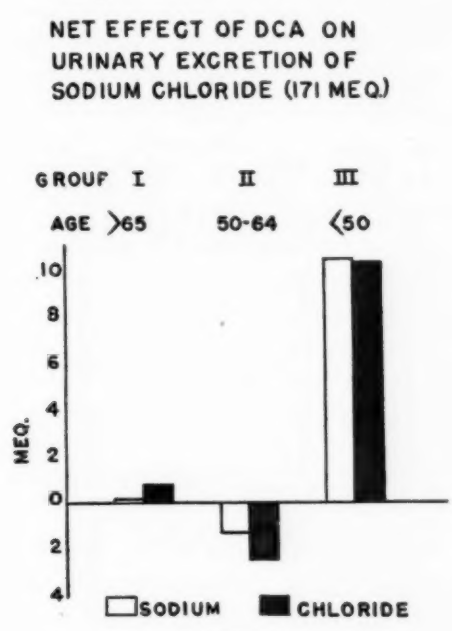

FIGURE 4

years of age. However, none of these differences proved to be statistically significant.

DCA caused a retention of some of the ingested sodium in the subjects of Group III (under 50 years of age), and the difference between this and the corresponding figures for the other two groups was highly significant, the value for T being about 2.9 and that for P approximately 0.01 (Table 2 and Fig. 4). Chloride behaved similarly to sodium (Table 2 and Fig. 4). The retention of ingested chloride under the influence of DCA was striking only in Group III, and the difference between this and the other two groups was a significant one, with a T value of 2.5 and a P of approximately 0.02.

DCA causes retention of sodium and, to a lesser extent chloride, in all age groups; but under the stress of added salt, older individuals respond to this action in a limited manner, if at all.

DISCUSSION

In the data presented, two facts stand out clearly: 1) younger individuals respond more vigorously than older ones to the sodium and chloride-retaining effects of DCA, and 2) DCA fails to cause the retention of any appreciable amount of a large single dose of salt in subjects over 50 years of age, whereas it exerts a characteristic effect in those under 50. What is the reason for these age differences? Among the possibilities deserving first consideration are alterations in adrenal and/or renal function.

If adrenal function is altered, it should be readily demonstrable by functional tests of that organ. In partial answer to the question, we have in all of the 50 subjects discussed, observed the response of the eosinophils to epinephrine (22). Although somewhat unreliable in our hands as a test of adrenal function, no differences have been noted in the responses, which could be attributed to age. In 19 of our subjects, we observed the responses of the circulating eosinophils to ACTH, according to the method of Thorn and his associates (23) as modified by Randolph (24). Simultaneously, we measured the urinary excretion of sodium, chloride and potassium for a two-hour period before and for a two-hour period after the injection of ACTH (22). In the 19 subjects, an increased excretion of sodium occurred in 15, of chloride in 14 and of potassium in 18. Age was not a factor in the result. These characteristic responses point to apparently normally functioning adrenals in older subjects. We are left with the conclusion that the variations in response to salt and DCA are due to changes in renal function and not to any failure on the part of the adrenal gland. Proof of such change during aging is not lacking, and by virtue of a rather ingenious technical procedure Shock and his associates have demonstrated a lowering of renal blood flow with a consequent over-all decrease in the excretory power of the kidney in older people (25).

We are particularly intrigued with the ability of salt-loading to negate the action of DCA in older individuals. With some modification, such a procedure might be employed as a routine test of the ability of aged persons to withstand stress. Thus far, efforts to obtain objective evidence of working capacity or ability to undergo stress have not been free of subjective and psychic influence in any age group. Furthermore, in older subjects, their use may induce some permanent physical impairment. The use of salt and DCA as employed here seems to be fraught with little danger, yet may sufficiently simulate the action of the adrenal to afford us a clinically useful gauge of the ability of tissues to respond to a shock-stimulus or stress.

SUMMARY

1. The influence of added salt (10 Gm.) and desoxycorticosterone acetate (10 mg.) upon the excretion of electrolytes has been observed in 50 subjects upon whom 71 tests have been performed. The data obtained have been analyzed in relation to the age of the subjects, in groups representing those over 65 years old, those between 50 and 64 and those under 50 years of age.

2. The administration of salt and/or DCA failed to influence materially the urinary volume and the excretion of uric acid, creatinine and 17-ketosteroids.

3. Age did not significantly affect the ability of the subject to excrete administered salt.

4. DCA caused a retention of sodium and chloride in all three groups of subjects, most marked in those under 50 years of age. The administration of salt depressed this effect, particularly in the two older groups.

5. Under the conditions of the test, DCA showed a slight tendency (not statistically significant) to increase the excretion of potassium.

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THE DIAGNOSIS AND TREATMENT OF AMEBIC DYSENTERY

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Bowel infections due to E. histolytica have been variously reported in this country to occur in from 3 to 30 per cent of the adult population. This wide spread in the reported incidence figures may be reconciled either by a lack of uniformity in the criteria for diagnosis, or differences in the type of population samples studied. The consensus is that a reasonable estimate would place the frequency at from 5 to 10 per cent of the adult population (1–4). Even this figure represents a rather significant incidence and provides adequate stimulus for reflection upon some of the enigmas of amebiasis.

Since 1946, 3,057 patients have been examined in our laboratory for E. histolytica infection. Twenty per cent of these patients have had complement fixation tests carried out for us in collaboration with the National Institutes of Health, Bethesda, Md., and the Communicable Disease Center, Chamblee, Ga. These data seem pertinent to specific considerations of this subject.

METHODS

The type of population sample. These patients were either ambulant or hospitalized, and were referred to the laboratory for study specifically because of the presence of active gastro-intestinal tract symptoms or fever of undetermined origin. This selected group cannot be considered analogous to that involved in a general-population or food-handler type of survey in which there are no presenting gastro-intestinal tract symptoms.

Pre-examination activities of the patients. No patient was accepted who within three weeks of the time of the examination had had barium studies of the gastro-intestinal tract, had received gallbladder dye, had had any sulfonamide or antibiotic therapy, or who was receiving any mineral oil, vegetable mucilage, methylcellulose, kaolin, or bismuth preparation. This prerequisite was deemed essential to eliminate potential effects of these preparations in altering the bacterial flora of the gastro-intestinal tract and the possible effects on amebic growth.

Criteria for diagnosis. It was required that characteristic cysts of E. histolytica be identified in the feces. If trophozoites only were found, a positive diagnosis of E. histolytica infestation was not made unless the trophozoites could be made to encyst by cultivation. In this regard we are in agreement with Rees (5) that there is no definite way to distinguish between the trophozoites of E. histolytica or those of E. coli, despite statements in the literature to the contrary. Stools were passed in the laboratory and were examined immediately. A series of two normally passed stools and a fluid cathartic specimen were routinely examined.

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RESULTS

Table 1 demonstrates the incidence of E. histolytica infections in our population sample of 3,057 subjects, using the foregoing criteria for diagnosis. Except for the year 1946, the relative constancy of incidence is of particular interest.

From our total laboratory population, 605 patients by random selection were given complement fixation tests.[1] These data are presented in Table 2. Of the 605 patients so studied, 245 showed positive results, either on fecal examination or by complement fixation test. This would represent an incidence of amebiasis of 40.5 per cent, decidedly high for any group sampling. The incidence of positive microscopic findings for this group was only 12.2 per cent. Although the chance for a negative microscopic finding associated with a negative complement fixation was greater than for any other combination (67.7 per cent), a positive

TABLE 1

Incidence of amebiasis among patients referred to the laboratory for study because of the presence of gastro-intestinal tract symptoms

Year	No. of patients examined	Stools showed E. histolytica	
		No. of patients	%
1946	481	17	3.53
1947	543	39	7.18
1948	526	39	7.41
1949	558	44	7.88
1950	577	53	9.18
1951	259	22	8.49
1952*	113	11	9.72
Total—or average.....	*3,057*	*225*	*7.36*

* Data for six months only.

microscopic finding associated with a negative complement fixation was obtained in 62.2 per cent.

These data may be summarized by the statements that: A reasonable estimate of the incidence of amebiasis in the adult population with gastro-intestinal tract symptoms in this area is about 7 to 9 per cent; the complement fixation test for amebiasis, as now being reported to the physicians in the United States, must be interpreted with great caution and is of limited, if any, diagnostic value. Reports on the efficiency of the complement fixation test by Fulton and Joyner in England (6), and by Kenny in this country (7), imply a greater correlation with fecal diagnosis. These differences may be explained by variations in the antigen and in the technique of the complement fixation tests with different groups. Apart from specific identification of characteristic E. histolytica cysts in a properly collected stool specimen, the only other diagnostic procedure

[1] Performed at The National Institutes of Health, Bethesda, Md., and the Communicable Disease Center, Chamblee, Ga.

of especial value is the routine proctoscopic examination of all patients with diarrheal disease. Approximately 5 to 8 per cent of our group had positive proctoscopic findings.

TABLE 2

Percentage of agreement between the results of the microscopic stool examination and the complement fixation test

Year	Microscopic (+)				Microscopic (−)			
	Complement (+)		Complement (−)		Complement (+)		Complement (−)	
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
1946	1	11.1	8	88.8	2	5.2	36	94.7
1947	3	42.9	4	57.1	2	8.3	22	91.6
1948	2	28.5	5	71.4	3	13.0	20	86.9
1949†	4	57.1	3	42.8	15	24.5	46	72.1
1950	8	32.0	17	68.0	68	31.4	148	68.9
1951	6	54.5	5	45.4	54	51.4	51	48.5
1952*	4	50.0	4	50.0	27	42.1	37	57.8
Total—or average	*28*	*37.8*	*46*	*62.2*	*171*	*32.3*	*360*	*67.7*

* Data for six months only.

† Tests on sera were run at the National Institutes of Health, Bethesda, Md., until May 1949. Subsequent tests were run at the Communicable Disease Center, Chamblee, Ga.

THERAPY

With the foregoing background of the problems associated with the diagnosis of amebiasis, it seems not unreasonable that there should be equally numerous problems of therapy. Knowledge of the growth characteristics of E. histolytica is essential to any discussion of growth prevention. It is well known that one of the great obstacles to research studies of the organism, is that E. histolytica cannot be grown in pure culture but requires the symbiotic activity of other organisms. In 1924, Hegner (8) observed that of the various animals in the Baltimore Zoo, the carnivores had no protozoa in their stools, the omnivores had a moderate number, and the stools of the herbivorous animals were loaded with all varieties of protozoa. Although the practical application of this observation on utilizing high-protein, low-carbohydrate diets in the treatment of patients with amebic colitis has not become a matter of record, we have been able to observe a few patients in whom amelioration of symptoms and negative stool cultures were obtained following such a diet. It would seem that the mode of action of a high-protein, low-carbohydrate diet is to alter the bacterial flora of the intestinal tract in such a way as to make further growth of the amebae difficult. It seems equally probable that the mode of action of some of the amebacidal drugs depends upon an alteration of the intestinal flora inhibiting continued growth of the amebae, rather than upon a direct effect on these organisms.

Regardless of the clinical stage of amebiasis or the extent of involvement, certain general concepts seem important in outlining therapy.

Prophylactic measures. In most communities it is forbidden by law for patients harboring E. histolytica in their stools to work as food handlers. Similar rigorous conduct is commonly ignored in the case of a housewife responsible for the meals for her entire family. Meticulous hand hygiene, instructions concerning the use of a nail brush, soap, and water must be emphasized. Restriction concerning the use of public swimming pools would likewise be in order.

Dietary measures. The avoidance of food items which notoriously increase gastro-intestinal tract motility is most helpful. It is important that departures in stool habit in patients undergoing therapy be properly interpreted. Frequently one cannot tell whether an episode of abdominal cramps or diarrhea is due to "something I et" or to a flare-up in the amebic process. Maintenance of the patient on a bland diet simplifies this problem and minimizes the potential irritant effects of certain food items on an already inflamed mucous membrane. The use of a bland high-protein, low-carbohydrate diet is recommended as both reasonable and practical, since it controls

a) Intestinal flora as related to amebic growth,

b) Irritant effects of ingested materials, and

c) Allows for a more critical interpretation of response to amebacidal therapy

Adjunct medication. The administration of antispasmodics tends to ameliorate some of the problems of altered motility, thereby assisting not only in relief, but in better interpretation of symptoms.

The treatment of specific phases of amebiasis.

a) The so-called "carrier-states," "cyst-passers" or lumen infestations are usually diagnosed during the course of some general survey or in the course of routine examination of food handlers. There is a considerable body of opinion, with which we concur, that E. histolytica may exist as a lumen parasite and not produce active symptoms. It is difficult to conceive of cysts being present without the co-existence of trophozoites. Whether trophozoites may live free within the lumen or whether they have to burrow into the mucous membrane in order to survive is a moot question. Because of the possibility that E. histolytica may occur as a lumen parasite without producing tissue invasion, it is imperative that the physician be certain that symptoms are unequivocally due to the infection. Exclusion of other gastro-intestinal tract lesions by roentgenographic and proctoscopic examination is essential. Similarly, because E. histolytica may be harbored in the bowel without the presence of significant gastro-intestinal tract symptoms, it does not follow that the so-called carrier state should not be treated. As a matter of fact, considerable ulceration may be present without much in the way of symptoms. I concur with Craig and Faust (9) that if the organism is present, therapy should be instituted, regardless of the presence or absence of symptoms.

Because of the availability of an absorbable amebacide, such as chloroquine, and its relative lack of toxicity as compared with emetine, it is my opinion that this nonsymptomatic group should receive both an absorbable and a lumen-acting drug, as in the case of active amebic infections.

b) The active phases of amebic infestation may be manifested in a variety of ways, of which a profuse sustained diarrhea, or intermittent bouts of diarrhea, are but two variations. The evidence suggests that these symptoms occur because of invasion and ulceration of the mucous membrane. On occasion the ulceration may be visualized by proctoscopic examination, but more frequently it may involve an area of bowel beyond any possible direct inspection. The important concept is that under these circumstances there is tissue invasion, and the administration of an agent which acts predominantly within the lumen and is essentially nonabsorbable, is not sufficient. The combined use of emetine and/or chloroquine plus one of the nonabsorbable amebacides is indicated.

c) The therapy of amebic invasion of the liver is already predetermined by the diagnosis. Lumen-acting, nonabsorbable amebacides are obviously not suitable. The use of either emetine or chloroquine or both is the procedure of choice. If there has been secondary bacterial invasion of the abscess, simultaneous use of one of the antibiotics (aureomycin, chloromycetin, terramycin, or streptomycin) is in order. Abscesses which do not rapidly disappear following emetine therapy should undergo surgical drainage.

Iodoxyquinoline compounds

These are mentioned first because they are the least toxic and have the widest range of usefulness.

Diodoquin. This is available in 0.2 Gm. tablets containing 63.9 per cent of iodine. The daily dosage is from 1.8 to 2.0 Gm. for twenty days. Repeated courses may be employed freely but, as with the other amebacidal drugs, adequate recheck stool examinations should be carried out. In chronic refractory cases, 0.6 to 1.2 Gm. of the drug may be given daily for periods of several weeks. There is some justification for the use of this drug as a prophylactic for individuals who are making trips into known endemic amebic dysentery areas. Two individuals in such a situation in Mexico, were maintained by the author on 0.6 Gm. daily for a period of two years without harmful effect. Untoward reactions may occur in iodine-sensitive persons, despite the fact that relatively little, if any, iodine absorption is supposed to take place from the bowel. On occasion, constipation or pruritis may occur following the administration of Diodoquin or any of the other iodine-containing preparations. Less purgative effect is generally observed during the use of Diodoquin than with the other preparations, because of the insolubility of the iodine.

Vioform. This is supplied in 0.25 Gm. tablets or capsules containing 41 per cent of iodine. The daily dosage is 0.75 Gm. per day for seven to ten days. It has been suggested that courses be repeated if necessary after a seven-day interval of rest. There would seem to be little reason for not employing this drug in larger dosage, especially in view of the lower iodine content.

Chiniofon. Chiniofon (sodium iodoxyquinoline sulfonic acid containing 26 to 28 per cent iodine) was first introduced by Muhlens and Menk in 1921 and was marketed under the proprietary name of Yatren. It is also marketed under the name of Anayodin. The dosage is the same as for Vioform, namely, 0.75 Gm. daily for seven to ten days. It is supplied in 0.25 Gm. tablets.

Arsenicals

Carbarsone. Carbarsone is available in 0.25 Gm. capsules; the dosage recommended is usually 0.50 to 0.75 Gm. daily for seven to ten days. Chemically, carbarsone is *p*-carbaminophenyl-arsonic acid and contains 28.85 per cent of arsenic. The toxicity of this drug is much greater than that of Vioform or Diodoquin, and the occurrence of nausea or exacerbations of diarrhea is more common than with the iodoxyquinoline derivatives.

Emetine

Emetine hydrochloride. Administered intramuscularly or subcutaneously this drug acts as a cumulative protoplasmic poison. Mattei (10) reported that emetine appeared in the urine within twenty to forty minutes after injection. It can continue to be detected in the urine for from five to nine weeks after therapy has been completed, implying "some kind of stable deposit in the body; perhaps at the site of injection." Although it is especially effective in amebiasis if there is evidence of tissue invasion, fatalities have been reported, as well as definite evidence of myocardial changes as manifested by electrocardiographic alterations. If electrocardiographic changes (depression or inversion of T waves, decreased amplitude of the QRS deflection, changes in conduction time, or changes in ST segment deflection) do appear, the drug should be stopped. In patients with a concomitant cardiac pathologic condition, and in patients in the older age group, electrocardiograms taken before and at intervals during therapy may serve to detect the occurrence of any toxic effect on the myocardium at the earliest possible moment. When used either intramuscularly or subcutaneously, despite care in selection of the injection site, tissue necrosis and sterile abscess formation may occur. Various procedures have been recommended, such as injection of 30 mg. twice daily, or injection of 60 mg. once daily. It is the consensus that not more than 600 mg. should be administered in a ten-day interval. Because clinical reports suggest that toxic manifestations tend to appear after the administration of 240 to 300 mg. in a four-day to five-day period, some clinicians prefer to give short courses more frequently, and stop emetine therapy at the end of five days after a total of 300 mg. has been administered. This is my own preference.

Antibiotics

Bacitracin. This may be had in 10,000-unit tablets for oral use. A final recommendation as to daily dosage level cannot as yet be made. Good results have been obtained with daily doses ranging between 50,000 and 100,000 units. Apparently no toxic effects have been reported after the use of the drug orally, even for long periods of time. In our hands, with only a limited series of observations, 100,000 units daily for a ten-day interval seemed to produce results equivalent to those obtained with some of the iodoxyquinoline derivatives. Other groups have reported a higher relapse rate than with the iodoxyquinoline agents.

Streptomycin. Administered orally, streptomycin has the ability to alter the bacterial flora of the gastro-intestinal tract. Various combinations of streptomycin have been used by the writer with satisfactory results. The efficacy of these preparations appears to be related to the effect on the bacterial flora of the intestinal tract, because during *in vitro* observations amebic growth is not appreciably altered. The dosage employed in our investigational studies was 100 mg. of streptomycin ten times daily.

Penicillin. Penicillin may alter bacterial flora of the gastro-intestinal tract, whether administered orally or parenterally. The inactivation of penicillin by the penicillinase elaborated by the colon bacillus makes it a poor selection as a therapeutic agent.

Aureomycin. Since the introduction of this antibiotic agent with a wide range of activity for numerous bacteria, some limited reports of its employment as an amebacidal agent have appeared. As with other amebacides, amebic growth is not inhibited in the test tube. The probable mode of action in the gastro-intestinal tract is by way of altering the established flora, thereby creating a growth environment incapable of allowing E. histolytica to survive. We have used aureomycin in doses of 0.250 Gm. every six hours for periods of two weeks in a limited group of patients. It is too early to evaluate any long-term results. The absorption from the gastro-intestinal tract would appear to make aureomycin one of the three such amebacidal agents (emetine and chloroquine being the other two) worth considering for administration to patients with evidence of tissue invasion.

Terramycin. Several groups have reported upon the efficacy of this antibiotic against E. histolytica, and these data seem analogous to those available on the use of aureomycin and Chloromycetin. Using a dosage of 1.0 to 2.0 Gm. for ten-day intervals, Tobie, *et al.* (11)

found terramycin effective in controlling an institutional epidemic of intestinal amebiasis. Although they likewise used aureomycin, they could not conclude that one was more effective than the other. Both of these drugs were thought superior to Bacitracin in doses of 40,000 to 80,000 units daily in this same epidemic.

Chloromycetin. Chloromycetin would appear to have a role in the therapy of amebiasis in terms of its effects on the bacterial flora of the gastro-intestinal tract. Reports of long-term observation following Chloromycetin therapy are not yet available and such observations would be of interest. The dosage would appear to be in the same range as when used for other purposes—0.25 to 0.5 Gm. every six hours for a period of from ten to fourteen days.

Fumagillin. Fumagillin is a new crystalline antibiotic isolated from a strain of Aspergillus fumigatus. Although effective against E. histolytica in vivo in animals, only a limited number of observations are available concerning its efficacy in human amebiasis. Dosage schedules of 20–75 mg. per day have been reported effective if administered over a fourteen-day period. Toxic dosages in animals result in destruction of the gastro-intestinal tract, with anorexia, vomiting, hemorrhage, and weight loss. Large doses produce tubular degeneration of the kidneys. It is described as effective on both cysts and trophozoites. As results of clinical trial appear and can be critically evaluated, this agent may prove to be a useful addition to our armamentarium. For the time being, use of the drug should be on an investigative basis.

Sulfonamides

A few reports have appeared suggesting some usefulness for the employment of the poorly absorbed or nonabsorbable sulfonamide preparations, such as sulfaguanidine and succinylsulfathiazole. Their mode of action probably is related to the inhibition of amebic growth resulting from alteration of the bacterial flora of the intestinal tract. The dosage varies between 6.0 and 12.0 Gm. a day.

Chloroquine

Chloroquine diphosphate (7-chloro 4/4-diethylamino-*l*-methylbutylamino quinoline diphosphate). This is one of the newer antimalarial drugs. It is almost completely absorbed from the gastro-intestinal tract and is apparently deposited in the various tissues, especially the liver, spleen, kidneys, and lungs. Approximately 10 to 20 per cent of the drug can be recovered in the urine, the remainder being metabolized by the body. Headache of varying severity, pruritis, and blurring of vision are some of the toxic manifestations. Manson-Bahr (12) has reviewed cases of amebiasis treated with chloroquine, including a case of amebic hepatitis which was refractory to treatment with other drugs. The dosage schedule recommended was 4.0 Gm. over a period of eight days, and a second course of 4.75 Gm. over a period of sixteen days. A priming dose of 0.75 Gm. may be given the first day and 0.25 Gm. twice daily for the remainder of the treatment period. It would seem that chloroquine is particularly appropriate in the treatment of patients with evidence of tissue invasion.

I have rather mixed feelings concerning the use of these antibiotics in the treatment of amebiasis. First, there is no really good critical evidence that they are distinctly superior to the iodoquinoline group of drugs. Second, the high incidence of gastro-intestinal tract irritation, with nausea, emesis, diarrhea, stomatitis and proctitis has precluded their use for many infections of short duration, when from seventy-two to ninety-six hours of adminstration is sufficient. The chief difficulty tends to arise when therapy must be extended longer than three to four days. The longer duration of therapy which is necessary for amebiasis emphasizes this difficulty. The treatment of a diarrheal disease with agents which themselves so frequently produce diarrhea seems to make the prob-

lem more complicated. Until someone is able to demonstrate a clear-cut superiority of these agents over the iodoquinolines, it is better to use the latter group.

The chief controversy between the various investigators in the field of amebacidal therapy seems to be when to use emetine. There is general agreement that when one variety of amebacide does not work, then another should be tried. Many of the recommendations obviously are arbitrary and represent empirical thoughts on the subject rather than critical evaluation of scientific evidence.

It seems to be the consensus that in the presence of hepatic amebiasis, hepatic abscess or other sites of involvement outside the gastro-intestinal tract, emetine is the drug of choice. Several groups are now using chloroquine in its place and with good results. The weight of opinion has favored the use of emetine in the case of early amebiasis with acute dysentery and fulminating symptoms. There is no reason why chloroquine should not be similarly used.

Whether or not an absorbable amebacidal agent such as emetine or chloroquine should be used on every patient who has been found to harbor E. histolytica in the stools, depends upon whether one considers the organisms (either trophozoites or cysts) to be living free within the bowel lumen. Failure to demonstrate invasion of the mucous membrane by clinical tests does not exclude the presence of such lesions. Because of the very low toxicity incident to chloroquine, and its great ease of administration as compared with emetine, it is now my practice to treat all patients in whom the diagnosis is established, first with chloroquine and then with the lumen-acting drugs.

Associated with concepts of therapy, there is always the decision as to when therapy should be discontinued. Between chloroquine and the lumen-acting drugs (the latter given in rotation) there should be approximately five to six weeks of intensive treatment. At this juncture, all therapy should be discontinued. The stools should be rechecked no sooner than four weeks after discontinuance of the drugs. If in this interval the patient adheres to the bland diet and the use of antispasmodics, much more can be learned about the interpretation of residual symptoms of bowel irritability, which are perhaps due to continued amebic activity.

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MANAGEMENT OF ARTERIOSCLEROTIC VASCULAR DISEASE OF THE LOWER EXTREMITIES, WITH PARTICULAR REFERENCE TO THE CONTROL OF INFECTION*

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Arteriosclerosis of the lower extremities is a progressive obliterative process which occurs predominantly in individuals over 40 years of age and is more common in males. Diabetes mellitus coexists with this disease in a substantial number of patients and, when present, poses a special problem because of the increased incidence and severity of infections associated with it. In its early stages peripheral arteriosclerosis may be asymptomatic, but as the disease progresses intermittent claudication, rest-pain, ischemic neuritis, infection, and gangrene may develop and cause the patient to seek treatment. Claudication and rest-pain are the result of anoxia in the muscles and deep structures of the leg, whereas ulceration and gangrene are associated with inadequate blood supply to the skin. Muscle and skin involvement may develop separately or simultaneously, but in advanced cases both are usually present. The severity and extent of these manifestations depend largely upon the state of the collateral circulation. If the latter is sufficient and can keep pace with the obliterative process in the main vessels, the limb remains compensated, providing episodes of acute thrombosis do not supervene. The margin of safety with regard to life or limb is often very narrow, and ill-advised maneuvers such as excision of bunions, toenails and plantar warts may initiate a disastrous sequence of events. A break in the continuity of the skin, whether due to trauma or to anoxic cellular death, is an ominous development, because infection in some degree is almost certain to follow. The necrotizing action of bacteria resulting in further thrombosis and reflex vasospasm is then superimposed on vascular insufficiency, thus providing additional mechanisms for the production of ulceration or gangrene. Certain extremities that would succumb to the combined action of vascular insufficiency and infection will survive, if the infectious component can be controlled.

Various medical and surgical measures designed for the relief of symptoms and the improvement of collateral blood flow to the leg are in current use. Patience and the judicious withholding of vigorous treatment are often more efficacious than aggressive measures. On the other hand, the appropriate timing of definitive surgical procedures is of the utmost importance, especially in the presence of infection. Various authors have discussed the treatment of infection as part of the

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management of peripheral arteriosclerosis but, exclusive of the diabetic group of patients, there is a paucity of information in the literature regarding the specific management of this aspect of the disease. We have come to regard the infectious component as a distinct pathologic entity which frequently can be dealt with separately and definitively. The initial therapeutic efforts should be directed toward the eradication of sepsis when it is present. Not only does this reduce the hazard of subsequent surgical procedures but it also removes a stimulus for reflex vasospasm, thereby improving the prospects for success in the management of the vascular component.

It is the purpose of this paper to review briefly methods of evaluation and treatment of this disease, with particular reference to certain preferences exercised in our clinic.

EVALUATION AND CONTROL OF THE INFECTIOUS COMPONENT

The failure of antibiotics to prevent the development and progress of infections associated with obliterative arteriosclerosis is due in part to the fact that insufficient concentration of the drug is carried to the tissues by the partly occluded arterial tree. Since antibiotics are not effective in the presence of necrotic tissue, its removal is necessary for successful therapy. The injection of antibacterial substances directly into the artery of an extremity has not appealed to us because of lack of convincing evidence of its efficacy and because of the danger of dislodging atheromatous plaques or inducing further vasospasm in a diseased vessel.

In our experience, the majority of the more severe infections persist and advance despite systemic antibiotic treatment. We have continued to use antibiotics systemically because they may be of considerable value in limiting invasive spread or in preventing septicemia, even though they do not always control the local process.

Moist applications of physiologic saline or Dakin's-type solutions are often effective, especially when the infection is of a saprophytic, non-invasive, superficial type. Frequently, however, severe infections fail to respond to such treatment. Lesions characterized by dry gangrene in which there is no infectious component should not be treated with moist applications, because they soften the eschar and afford a portal of entry for bacteria. Such lesions should be covered with dry sterile dressings.

Inability to secure adequate tissue levels of antibiotic by systemic administration suggested the possibility that certain persistent infections might respond to a combination of systemic and local use of antibacterial agents. Topical therapy as commonly applied frequently meets with failure and has been regarded with disfavor by many surgeons. Others, however, have found it helpful in the management of certain conditions such as osteomyelitis, burns, eczema and impetigo. We have used it, pending wound closure, to prevent local recurrence of sepsis following excision of severely infected tissue, and to prepare ulcerated surfaces for early skin grafting. An analysis of the reasons for failure led us to experiment with various techniques for the applications of topical therapy and to adopt certain requisites which we consider necessary for its successful use. These requi-

sites are 1) absence of necrotic tissue, 2) susceptibility of organisms to the antibacterial agent, 3) adequate constant contact between the drug and the site of infection, 4) prevention of recontamination with resistant organisms, and 5) use of agents which are not inhibited in the wound and are well tolerated by tissues.

A study of a group of 21 patients with peripheral arteriosclerosis was conducted, in which a special effort was made to control the infectious component of the disease by a combination of surgery with systemic and topical antibiotic therapy. This work has been reported elsewhere in detail (1). The technique of dressing and the results of therapy are summarized here.

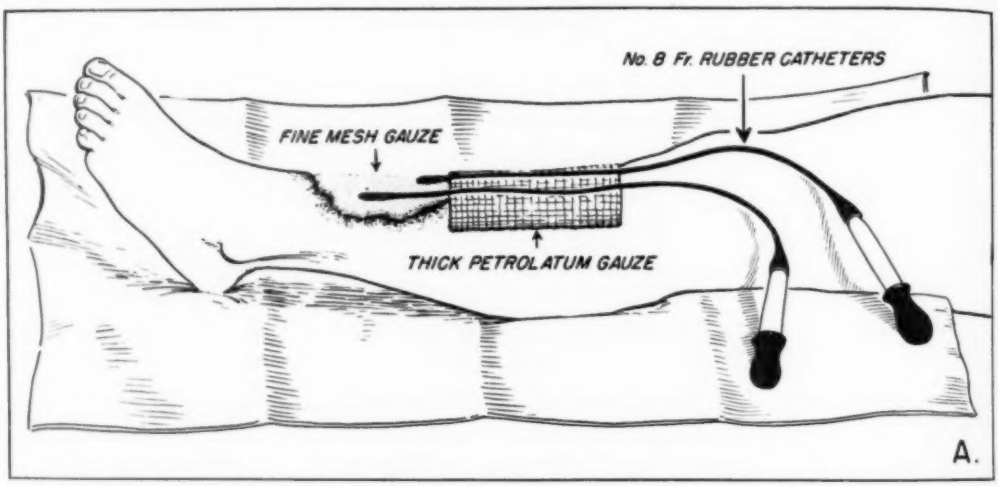

FIG. 1. A layer of fine mesh gauze is placed over the lesion, thick enough to act as a reservoir for the antibacterial solution but not so bulky as to hold the medication away from the lesion by absorption. Catheters for the instillation of medication are prevented from grooving the skin and starting new ulcerations by a thick underlying sheet of petrolatum-gauze strips. Sterile medicine droppers are inserted into the open ends of the catheters to facilitate aseptic injection of medication by puncturing the rubber bulb with a hollow needle. They are protected with sterile gauze between injections. (Reproduced with permission from Howe and Wigglesworth (1).)

Method of dressing. Surgical masks and sterile gloves and drapes were used during all dressings. In most instances adequate debridement could be carried out on the ward, but very painful lesions or those with an excessive amount of necrotic tissue were debrided in the operating room under anesthesia[1]. A layer of gauze trimmed to fit the geographic pattern of the debrided lesion was then placed so as to act as a wick to carry the medication into all crevices (Fig. 1). Since bulky gauze dressings soak up the antibiotic solution and keep it out of the wound, thin, accurately placed gauze was used. This gauze was easily saturated with small amounts of antibiotic solution fed to it through one or more number 8 or 10 French rubber catheters laid on the wick. Since slight pressure from the outside bandage on a rubber catheter may groove the skin and start a new ulceration in extremities with a poor vascular supply, a generous protective thickness of petrolatum gauze was placed beneath each catheter in the area where it came in contact with the skin. An additional sheet of well-lubricated petrolatum gauze was then placed over the whole area (Fig. 2). Another

[1] Extreme caution is advocated in attempting surgery on limbs with severe arterial occlusion.

more bulky layer of gauze was then placed outside the petrolatum strips and covered with sterile rubber sheeting or plastic material (Fig. 3). The purpose of this was to make the dressings as waterproof as possible and prevent evaporation of the solution[2]. The catheters

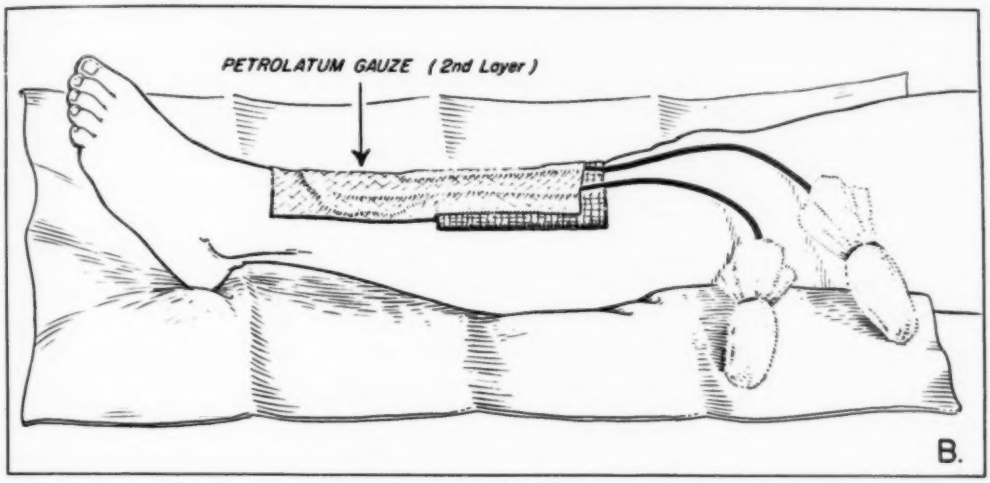

FIG. 2. An additional generous layer of petrolatum gauze is placed over the catheters to hold them in place and help make the dressing waterproof. (Reproduced with permission from Howe and Wigglesworth (1).)

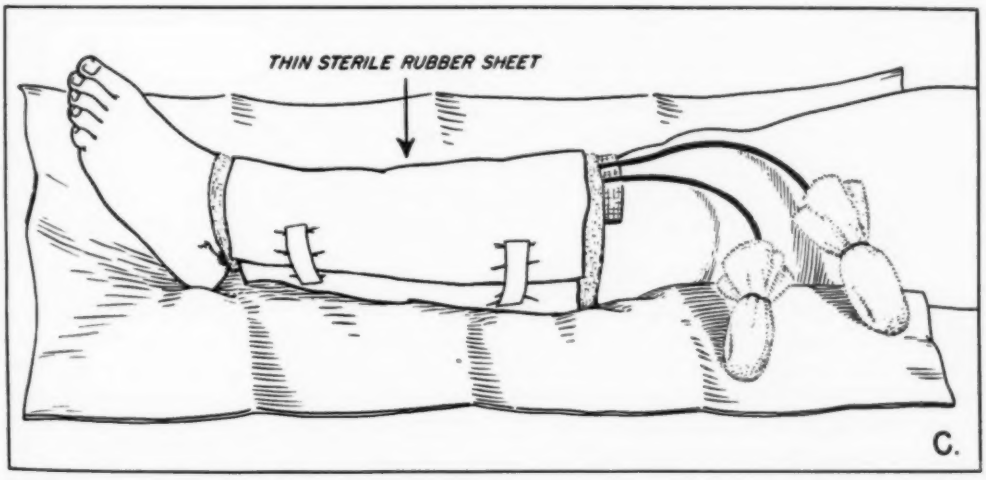

FIG. 3. A layer of rubber or plastic sheeting is incorporated into the dressing to make it as waterproof as possible and prevent recontamination of the wound by permeation of organisms through the dressing. (Reproduced with permission from Howe and Wigglesworth (1).)

were brought out through a final outer layer of loosely applied bandage, which served to hold the rubber sheet in place. Sterile medicine droppers were inserted into the open ends

[2] Colebrook and Hood (2) have shown that organisms (especially motile ones) can rapidly penetrate a wet dressing and contaminate the wound. This is prone to occur where the wet dressing comes in contact with the bed clothes, attendants' hands, or other contaminated objects.

of the catheters (Fig. 4). Antibacterial solutions chosen with the aid of *in vitro* sensitivity tests were injected with a needle and syringe by puncturing the sterilized rubber bulb of the medicine dropper. Two to 4 ml. of solution, depending on the size of the lesion, were introduced into each catheter every four to six hours. This kept the wound wet and in constant contact with a fresh supply of the antibacterial agent. Since such small amounts were administered, much of the solution remained in the bulb or in the catheter unless it was blown through with air after each injection. Dressings were left in place from four to six days before removal. It was observed that the maximal effect of topical therapy was usually accomplished within this period and that nothing further was gained by more prolonged therapy.

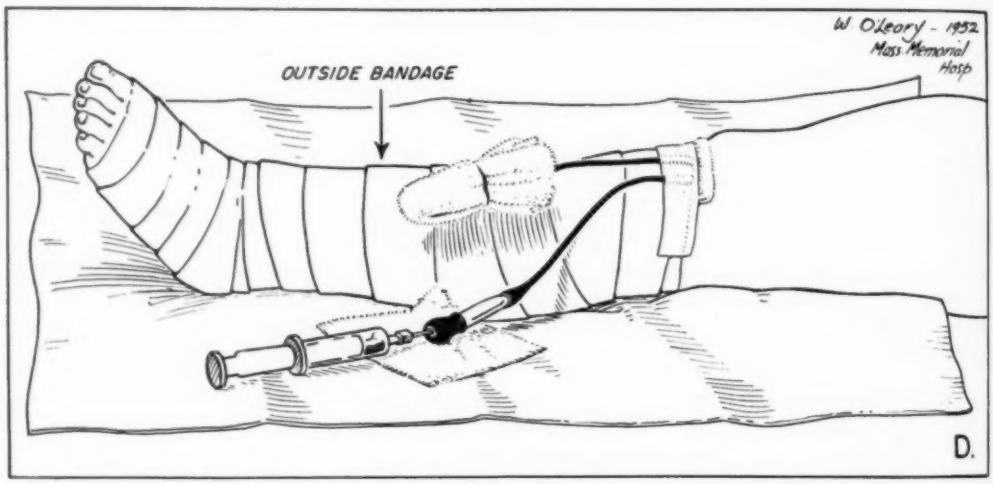

FIG. 4. Catheters are led through an outside layer of loosely applied bandage. Dressings are left in place from four to six days. Injections of 3 to 5 ml. of antibacterial solution into each catheter every four hours will keep the lesions constantly moist with a fresh supply of the chosen drug. The waterproof nature of the dressing prevents evaporation and allows treatment with small inexpensive amounts of antibiotics. (Reproduced with permission from Howe and Wigglesworth (1).)

Although in a few instances minimal wrinkling of the surrounding normal skin was present upon removal of the dressing, maceration was not a problem. It is known that application to the skin of certain substances, such as petrolatum, may produce obstructive anhidrosis and that warm environments may exacerbate inflammatory changes at these sites. This phenomenon was not encountered in our cases, perhaps because of diminished sudomotor activity in the atrophic skin of these patients. In order to minimize sudomotor activity and to prevent an increase in metabolic demands, the application of heat was avoided and precautions taken to maintain an optimal environmental temperature for the extremity under treatment. No instance of sensitivity from the localized topical application of drugs was seen. An occasional patient, however, may be allergic to rubber or plastic, and contact between the skin and the sheeting was prevented by an intervening layer of gauze.

Results. For purposes of classification the patients were divided into three groups, depending upon the relative predominance of the infectious or vascular component of the disease. All except 1 patient had received a previous course of penicillin, streptomycin or one of the broad-spectrum antibiotics systemically. This therapy was continued and in addition topical antibacterial treatment, as

previously outlined, was instituted. Agents were selected with the aid of sensitivity tests, but a solution of Sulfamylon and streptomycin[3] was found to be the combination of choice for topical application in over half the cases (1). The concentrations of various antibacterial solutions that may be used without causing injury to tissue have been discussed in previous articles (1, 3–5).

The first group consisted of 4 patients in whom vascular damage was minimal and infection was the predominant feature. Cultures showed mixed Gram-positive and Gram-negative flora in 2 cases and only Gram-positive organisms in the other 2 cases. The time required to control the infection ranged from two to thirteen days, with an average of five days. Following control of the infection, skin grafts were required in 2 instances but no sympathectomies or amputations were necessary. The time required for complete healing averaged twenty-five days.

The second group included 9 patients in whom both infection and vascular insufficiency were present. These combined factors threatened the loss of a limb, but the vascular component alone was not a great hazard. All but 1 lesion contained mixed Gram-positive and Gram-negative bacteria; this 1 lesion yielded a pure culture of Pseudomonas (4). Seven of the lesions in this group were in the soft tissues of the leg above the ankle. Pain, which was a prominent feature, was dramatically relieved by control of the infection. The clinical response in this group was most satisfactory, and the time required to control the infectious component ranged from four to eighteen days, with an average of eight days. Following control of the infection it was necessary to perform lumbar sympathectomy on 4 patients, a low thigh amputation on 1, and skin grafts on 3. The time required to obtain a definitive end-result following control of the infection ranged from seventeen to one hundred and three days, with an average of forty-seven days. The control of the infectious component, therefore, required a relatively short time in comparison to control of the vascular component.

In the third group were 8 patients in whom vascular insufficiency was the predominant feature. These limbs exhibited either dry gangrene without sepsis or extensive mixed infection involving bone, tissue planes or tendon sheaths. Four of these patients received systemic and topical therapy as described, and the infections were controlled in an average of five days. The vascular damage was so extensive that, despite control of the infection, amputation was advised for all 4 of them. Three patients were initially presented to us for treatment of an infected amputation stump. The last patient had sepsis of the foot in tissue planes which made it anatomically impossible to conform to the requisites for topical therapy. In the whole group there were 4 thigh amputations, 1 transmetatarsal amputation and a removal of the great toe. Two patients refused amputation and left the hospital. The time required from the beginning of treatment to complete stump healing was twenty days.

In every instance in which clinical control of the infection was accomplished there was a reduction in the bacterial flora, not only in relation to the total

[3] Five per cent Sulfamylon, containing 200 units of streptomycin per ml.

number of strains present, but also to the number of bacteria in each of the persistent strains.

In the group of cases with minimal arterial disease, the addition of topical antibiotics to the therapeutic regimen served to bring otherwise persistent infections promptly under control.

In the second group of cases, in which the infectious and vascular components of the disease were relatively equal, the combination of proper surgical care with systemically and topically administered antibiotics controlled the infectious component of the disease. In all instances in both of these groups the infections persisted until specific topical therapy was added to the therapeutic regimen.

In the third group of patients, in which the vascular component was predominant, chemotherapy appeared to be of no value in the control of the local infection when the requisites for topical therapy could not be fulfilled. When the requisites could be satisfied, however, the infectious component was controlled, but this did not heal the lesion or obviate the necessity for amputation.

The results indicated that the addition of properly applied topical therapy to good surgical care and systemically administered antibiotics is a useful adjunct, especially in the first two groups of patients. It was apparent that control of the infectious component of the disease, when possible, required a relatively short time in contrast to control of the vascular component. Following eradication of the infection, the necessity for vascular surgery depended upon the evaluation of the degree of underlying arterial disease.

EVALUATION OF THE VASCULAR COMPONENT

In the evaluation of an extremity with obliterative vascular disease, rest-pain, night cramps, claudication and the walking distance required to induce it, are important points. In the examination of the limb, atrophy, rubor, ulceration and gangrene should be looked for. There are three basic factors which must be considered in order to define accurately the vascular status of an extremity, as well as the indications for surgery. These are:

1) the state of the peripheral pulses,
2) the amount of vasomotor activity present,
3) the state of the collateral circulation.

State of the peripheral pulses. Careful palpation of the femoral, popliteal, anterior tibial, dorsalis pedis and posterior tibial arteries should be carried out, to determine whether their pulsations are present and normal, present but diminished, or absent.

Amount of vasomotor activity present. Vasomotor activity is a manifestation of an intact sympathetic nervous system and is present in all normal extremities in varying degrees. Although the best results following sympathectomy are obtained in patients with marked vasospasm, even a slight degree of vasomotor activity may be sufficient to upset a precariously balanced circulation. Since the warmth of the skin is dependent in large part upon the rate of blood flow through it, the measurement of skin temperature affords a convenient means of determining the influence of vasomotor activity upon peripheral circulation. Several

techniques are available which utilize this principle. Temperatures may be determined by a simple mercurial thermometer, but more accurate readings are obtained with thermoelectric devices.

One method measures temperature changes following diagnostic nerve blocks with procaine. A rise in the temperature of a digit following spinal, peripheral nerve, or paravertebral sympathetic block is a fairly reliable indication of release of vasoconstriction (6).

A centrally induced reflex rise in skin temperature of a digit following the application of heat to a distant area of the body is another method of studying vasomotor activity (6).

A third method, used routinely in our clinic, makes use of mild temperature stimulation in both directions, by employing warm and then cool environments. The patient is placed in a constant-temperature room at 83°F. and after one hour's exposure, skin temperature readings are recorded. The test is then repeated in a cool room at 68°F. In general, low digit temperature readings indicate greater vasomotor activity, whereas high digit temperature readings indicate less vasomotor activity. For example, if the digit temperature is below room temperature in both environments, the extremity exhibits the greatest degree of vasospasm. On the other hand, if the digit temperature in the cool room is 80°F. or higher, and in the warm room is 88°F. or higher, the extremity exhibits little or no vasospasm. Intermediate degrees of vasomotor activity lie between these two extremes.

On the basis of data obtained from the examination of the peripheral pulses and skin temperatures, patients may be classified into groups indicative of the state of their peripheral circulation. Experience has shown that, in the selection of candidates for sympathectomy, this information may be utilized with a high degree of accuracy in predicting the likelihood of beneficial results. Details of this method of study and classification have been reported by Smithwick and associates (6, 7, 8).

State of the collateral circulation. Probably the most important single factor in the evaluation of peripheral vascular disease is the state of the collateral circulation. We have found a simple bedside test, based on flushing and venous filling times, to be a satisfactory and reliable method (6). The collateral circulation is considered adequate if, after blanching on elevation, flushing of the toes on dependency begins in twenty seconds or less. Filling of the veins on the dorsum of the foot in thirty seconds or less is also evidence of adequate collateral circulation, providing the saphenous veins are competent. Flushing time is the more reliable test (6). Pain at rest is indicative of poor collateral circulation.

GENERAL MANAGEMENT

Foot care. The feet should be washed daily and lanolin applied. Epidermophytosis must be eliminated, lest a crack in the skin be a site of entrance for an invasive infection. Undecylenic acid or Whitfield's ointment is suitable for this purpose. Thick socks and well-fitting shoes should be worn and the feet kept warm in the winter. The prevention of trauma is most important. The nails

should be carefully trimmed and preferably cut straight across rather than rounded.

Exercise. Vascular exercises of the Buerger-Allen type may be helpful. The elevation phase should be short. It should never be longer than the time required for the foot to blanch and in some instances may be only fifteen seconds or less. Some authors advocate elimination of the elevation phase entirely and utilize only the dependent and horizontal phases. Schedules should be individualized.

Smoking. The elimination of smoking is advisable, especially in younger patients.

Drugs. The use of various vasodilator drugs has received a wide clinical trial in recent years. In general, the results have been disappointing. Regional sympathectomy remains the best way to improve circulation locally without producing the unfavorable effects of generalized vasodilation. Night cramps may be relieved by 0.3 to 0.6 Gm. of quinine or 50 mg. of Benadryl taken two to three hours before bedtime.

OPERATIVE MANAGEMENT

Lumbar sympathectomy. Until recently, this operation was employed largely in patients with obvious vasospasm and was not used extensively in arteriosclerotics. It is now apparent, however, that it is a worthwhile procedure in an appreciable number of these patients (9). Some authors are liberal in their indications for sympathectomy, whereas others are conservative and advise operation only under circumstances in which it is almost certain to be worthwhile.

The rationale for sympathectomy is to relieve vasospasm in the peripheral vasculature in order to stabilize blood flow at a higher rate. It is not necessary that this operation be limited to extremities exhibiting abnormally high vasomotor activity, since elimination of even minimal vasoconstriction may make a significant difference in a borderline circulation.

In general, patients having extensive main-vessel obliteration must also have a high degree of vasospasm if the best results are to be obtained following sympathectomy. Conversely, individuals with minimal main-vessel obstruction will respond favorably when slight vasospasm is present. Selection of only those patients with adequate collateral circulation will preclude operations which, although harmless, are of questionable benefit. The absence of an adequate collateral circulation, however, does not imply that sympathectomy will precipitate gangrene when none existed previously. The available evidence suggests that thrombosis, rather than the opening of arteriovenous shunts, is the precipitating factor in the uncommon instances in which gangrene has followed this operation (10). Such thromboses are nonspecific and may follow any type of surgery.

Sympathectomy is reported to improve intermittent claudication to some degree in from 10 to 75 per cent of patients. Six to twelve months may be required, however, before benefit is apparent.

Contraindications to sympathectomy include general debility consequent to coexisting cerebral, coronary or visceral arteriosclerosis, a rapidly advancing infectious process, extensive gangrene, and severe rest-pain.

The operation may be performed in one or two stages, through either a posterior or an anterior retroperitoneal approach. Morbidity is low, convalescence is rapid and mortality is practically nil.

Nerve crushing. Crushing of the peripheral nerves of the lower extremities is occasionally a useful procedure for the control of severe pain associated with an open lesion. It results in a peripheral sympathectomy which may speed up the healing process. The operation must be performed with meticulous technique, and an exact knowledge of the neuro-anatomy of the leg is essential (6).

Skin grafting. When small areas of gangrene appear in the skin proximal to the feet, excision and skin grafting may be necessary. The control of infections associated with these lesions has already been discussed.

Amputations. At times, the local removal of dead or infected toes will solve a particular vascular problem and render a more extensive amputation unnecessary. Collateral circulation must be adequate at the amputation site, if healing is to occur.

In recent years the procedure of *transmetatarsal amputation* has been advocated by various surgeons in an effort to avoid more radical procedures (11). It has been used, particularly in diabetics, when controllable infection is a major factor. The use of antibiotics has been of great value in enlarging the scope of this operation and reducing the incidence of failure. The selection of patients for transmetatarsal amputation requires a nicety of judgment. If infection can be eradicated and the collateral circulation is good, the outcome is usually successful. When the vascular component is predominant and the problem is mainly one of distal necrosis, selection is difficult. The persistence of rest-pain after a sympathectomy and several weeks in bed, indicates that the collateral circulation is in all likelihood inadequate for a successful transmetatarsal amputation. In the absence of rest-pain and with the infection controlled, the problem becomes one of the adequacy of the collateral circulation *at the site of the proposed amputation.* Sympathectomy, followed by a waiting period of several weeks, may be necessary in order to decide whether the circulation has been improved sufficiently to warrant transmetatarsal amputation. The technical aspects of this operation are of particular importance. Extreme gentleness in the handling of tissue is essential. The slightest unnecessary trauma may result in failure, even in the presence of an adequate collateral circulation. The use of forceps on the skin, unnecessary undercutting of flaps, hematomata, tension on the flaps, and dead space must be meticulously avoided. Sutures must be tied loosely, left in place at least two weeks and removed gently and in stages. Ambulation is delayed for several weeks. Rigid adherence to these criteria for selection and technique result in successful healing and a serviceable foot in 70 to 85 per cent of cases.

A *thigh amputation* is the procedure of choice when a more radical procedure is necessary. A simple circular incision without skin flaps is satisfactory and results in the lowest incidence of failure.

Endarterectomy. In recent years the procedure of endarterectomy with removal of arteriosclerotic plaques and resuture of the vessel wall has been carried out (12). The operation is still in the stage of clinical investigation and its usefulness is yet to be defined conclusively.

Resection of occluded segments. The procedure of resection of obliterated arteriosclerotic segments and their replacement with vascular grafts is currently being performed (12). Either venous or arterial grafts may be employed for this purpose. This procedure is also still in the investigative stage.

SUMMARY

Principles and methods of evaluation and treatment of arteriosclerotic vascular disease of the lower extremities have been reviewed.

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INTRAORAL CANCER AND THE USE OF CHEWING TOBACCO*

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In recent years considerable interest has developed concerning the apparent concomitant increase in the use of tobacco and increase in the incidence of lung carcinoma. Several recent and rather comprehensive reports in England (1), Germany (2) and the United States (3, 4, 5) indicate an apparently significant correlation between the development of pulmonary carcinoma and the long-time habit of heavy cigarette smoking. Currently the American Cancer Society is conducting an investigation of the smoking habits of over 200,000 men between the ages of 50 and 69—the age group with the highest death rate from lung cancer. Annual follow-up interviews will be obtained for three or four years, after which time the data will allow statistically-significant conclusions to be reached.

The several other forms of tobacco usage which have been implicated as possibly carcinogenic include betel nut-chewing tobacco mixtures (6), pipe smoking, and oral snuff or chewing tobacco. In addition to clinical and experimental investigations concerned primarily with the possible carcinogenic properties of tobacco smoke, there is a real need to elucidate the effects of direct application of tobacco to the oral mucosa. Clinically, the possible association of the use of chewing tobacco with the subsequent development of oral cancer has been mentioned by many writers. In 1915, Abbe (7) noted that all but 1 of 90 patients with cancer of the mouth were habitual users of tobacco in some form; unfortunately the clinical data appended were somewhat incomplete, but it was mentioned that in 13 instances the carcinoma developed at the quid-site.

The famous cancer pathologist, James Ewing, noted in his book (8) that tobacco was a predominant influence in the development of cancer of the buccal mucosa. Similarly, Martin and Pflueger (9) listed tobacco as a chronic irritant associated with carcinoma of the buccal mucosa.

Interestingly enough, the most important premalignant lesion of the oral cavity, leukoplakia, has also been considered to be closely associated with the use of tobacco by many clinicians. Fox (10) considered tobacco to be the most important irritant resulting in leukoplakia.

The observations such as those in the preceding paragraphs have been noted in the University of Minnesota Hospital Tumor Clinic for many years and incorporated in lectures to the medical students, without any serious attempt to prove their validity. In common with most clinicians, we considered the problem to be of minor importance. Our attitude was changed by finding that the annual

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production of chewing tobacco in the United States exceeds 40,000,000 pounds and that carcinoma of the oral cavity causes approximately 4 per cent of the deaths attributable to cancer. Certainly if such a preventable circumstance as the chronic use of tobacco could be proved to be associated with the development of oral cancer, public education might result in a substantial decrease in these lesions. Further, intensive laboratory investigation to isolate the carcinogenic factor or factors would be indicated. Such studies would have to be set up so as to negate the influence of other suggested causes of oral cancer, such as the chronic irritation of jagged teeth and dentures, infection, and the all-inclusive condition of poor oral hygiene. The importance of the general factor of constitutional tissue susceptibility cannot be overlooked. Separation of the effects of these conditions is not always possible, as illustrated by Figure 1.

Since 1951 all male registrants 50 years of age or older have been personally interrogated as to their use of tobacco. More specifically, the length of time pipe smoking, cigar and cigarette smoking, and snuff and chewing tobacco was used, and the site at which the pipe, cigarette, or quid was held were carefully noted. When possible, the deliberate re-checking of random interviews was accomplished in order to check the accuracy of the survey. The chief error detected was denial by the patient that he used tobacco, because he had ceased using it at some prior time. For example, several patients had chewed tobacco for many years, then stopped because of soreness in the mouth.

The present analysis consists of interviews of patients with oral carcinoma, oral benign lesions, skin cancers of the face and scalp, and miscellaneous soft tissue tumors; and additional control groups of patients with hernias and other benign surgical conditions.

It is noteworthy that a minimum age of 50 years was selected. Actually, very few carcinomas of the mouth were excluded by this selection, with the few exceptions of lesions appearing in men of the third and fourth decade. A majority of these excluded lesions did not seem to be related to tobacco or to any other etiologic agent such as jagged teeth, or poor hygiene. It should be mentioned, however, that numerous instances of oral leukoplakia were excluded by this age restriction; cases of leukoplakia are frequently associated with habitual tobacco-chewing, as revealed by the occurrence of the lesion at quid-sites. Many such lesions were thick, rough, verruciform and, in our opinion, would definitely have progressed with further stimulation into frank malignancies. In summary, the minimum age of 50 was chosen because clinical experience has indicated that carcinoma of the mouth associated with the use of tobacco develops only after fifteen or more years of continuous exposure of the mucosa.

In keeping with the foregoing premise it was arbitrarily decided to include as "chewers" and pipe and cigarette smokers, only those men with an habituation of over twenty years. This served two purposes: 1) selection or isolation of only those men with a sufficient period of exposure to tobacco, and 2) lessening of the necessity to attempt differentiation of the amounts of tobacco used, since it was felt that even slight indulgence over a period of ten years would summate to more than the minimal amount of "carcinogen" necessary to provoke malignancy.

Men who used tobacco less than ten years were all considered as non-chewers or non-smokers in this analysis.

Finally, it should be pointed out that the term "intraoral carcinoma" as used in this study includes only lesions of the alveolar ridges, floor of the mouth, and buccal mucosa; carcinomas of the lip, tongue, palate and tonsils are excluded. In

FIG. 1. This 73-year-old patient presented himself at the Tumor Clinic with a large fungating lesion of the right cheek which had been present about nine months. He gave a history of chewing snuff for about fifty years. No single site was indicated other than the alveolar ridge-buccal sulcus. Oral examination revealed particles of tobacco still in the interstices of the tumor. Also noteworthy was the presence of a single tooth directly adjacent to the lesion. Thus this patient amply illustrates the presence of multiple factors often said to be tumor-provoking.

a few instances of large fungating lesions it was difficult to judge whether the original site had been the buccal mucosa or the more common site—the vermilion border. Such cases were arbitrarily designated carcinoma of the lip.

Table 1 summarizes our experience, as limited and shaped by the strictures outlined in the previous paragraphs.

The highly significant correlation between carcinoma and leukoplakia of the mouth and the use of snuff and chewing tobacco is evident. The contrast to a group of patients with benign diseases is even more important, since almost a third of the latter patients chewed tobacco. This experience is not unique when one considers the age, nationality (predominantly Scandinavian) and economic selection.

TABLE 1

*The Association of the Use of Snuff and Chewing Tobacco with Tumors of the Face, Lip and Oral Mucosa**

Site of Lesion	No.	Chewers	Non-chewers	x^2	P
Benign disease	38	12	26		
Ca. of face	93	49	44	4.03	.02–.05
Ca. of lip	72	39	33	4.28	.02–.05
Ca. of mouth	40	26	14	8.73	<.01
Oral leukoplakia	23	18	5	10.69	<.01

* A probability (P) value of less than .03 is "significant" and a value of less than .01 is "highly significant."

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TABLE 2

*The Association of Pipe Smoking with Tumors of the Face, Lip and Oral Mucosa**

Site of Lesion	No.	Smoker	Non-smoker	x^2	P
Benign disease	38	18	20		
Ca. of face	93	40	53	.06	.8
Ca. of lip	72	33	39	.00	—
Ca. of mouth	40	14	26	.77	.30–.50
Oral leukoplakia	23	14	9	.57	.30–.50

* A probability (P) value of less than .03 is "significant" and a value of less than .01 is "highly significant."

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To a lesser degree, patients who were "chewers" also had a greater incidence of cancer of the lip and face. This relationship of the use of chewing tobacco and the occurrence of facial cancer is rather puzzling and has not been completely explained. Examinations of pipe and cigarette smokers for evidence of increased cancer of the lip and face gave negative findings (Tables 2 and 3).

Table 2 reviews a similar analysis of the possible cancerogenic effects of long continued pipe-smoking. It is evident from this table that there is no statistically significant correlation between pipe-smoking and carcinoma of the face, mouth or lips. In this regard, it is interesting that many clinicians have alluded to cancer of the lip as a pipe-smoker's cancer.

Table 3 depicts the association of the same malignant lesions with cigar and cigarette smoking. Again it is evident that among this group of patients there was no significant relationship of smoking to the presence of oral and facial cancer.

TABLE 3

*The Association of Cigar and Cigarette Smoking with Tumors of the Face, Lip and Oral Mucosa**

Site of Lesion	No.	Smoker	Non-smoker	χ^2	P
Benign disease	38	20	18		
Ca. of face	93	31	62	3.45	.05–.10
Ca. of lip	72	28	44	1.39	.20–.30
Ca. of mouth	40	15	25	1.15	.20–.30
Oral leukoplakia	23	11	12	0.39	.50–.70

* A probability (P) value of less than .03 is "significant" and a value of less than .01 is "highly significant."

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DISCUSSION

Chewing tobacco

In addition to several general articles concerned with a possible relationship of tobacco-use to cancer, which were referred to earlier, a few investigators who have dealt with the problem directly deserve mention.

Friedell and Rosenthal (11) reviewed both the clinical and the experimental literature on the tobacco-cancer problem. Their own study consisted of 8 patients with oral carcinoma—6 with buccal involvement and 2 with lesions of the alveolar ridge. These authors emphasized several important common factors which were also noted in the present study. First, all of their patients were over 60 years of age and had been chewing tobacco for many years (average, fifty years). Second, they emphasized the close relationship of leukoplakia to the subsequent development of malignancy. The lesions were described as having developed slowly, even over a period of several years. Our experience is similar.

A third important observation was that the lesions were often very tender and sore early in their development. In the course of the many interviews necessitated by this study, the complaint of soreness of the quid-site seemed most common in those patients in whom there developed thick, rough areas of leukoplakia and in whom malignancy subsequently occurred most frequently. In contrast, other patients visiting the clinic for other reasons had a history of indulging in snuff-chewing (same brand) for an equal period of time without ever noting any soreness. These patients *very seldom* had more than a slight filmy, white reaction at the quid-site. Thus it would seem that the patients who react most strongly to the presence of tobacco (Fig. 2) are those in whom malignancy is most likely to develop. This clinical impression awaits further substantiating data and is only appended because of its general interest. Attempts to elucidate the possibility of an allergic reaction in the affected patients will be mentioned later.

In our series of patients there were several instances of seemingly multiple primary oral carcinomas which developed over a period of many years. For example, in one patient a carcinoma of the left lower alveolar ridge originally developed where he had customarily held his quid of snuff. This lesion was treated by a combination of irradiation and surgery. When the patient was next seen, an obvious carcinoma of the right lower alveolar ridge was present—at the exact

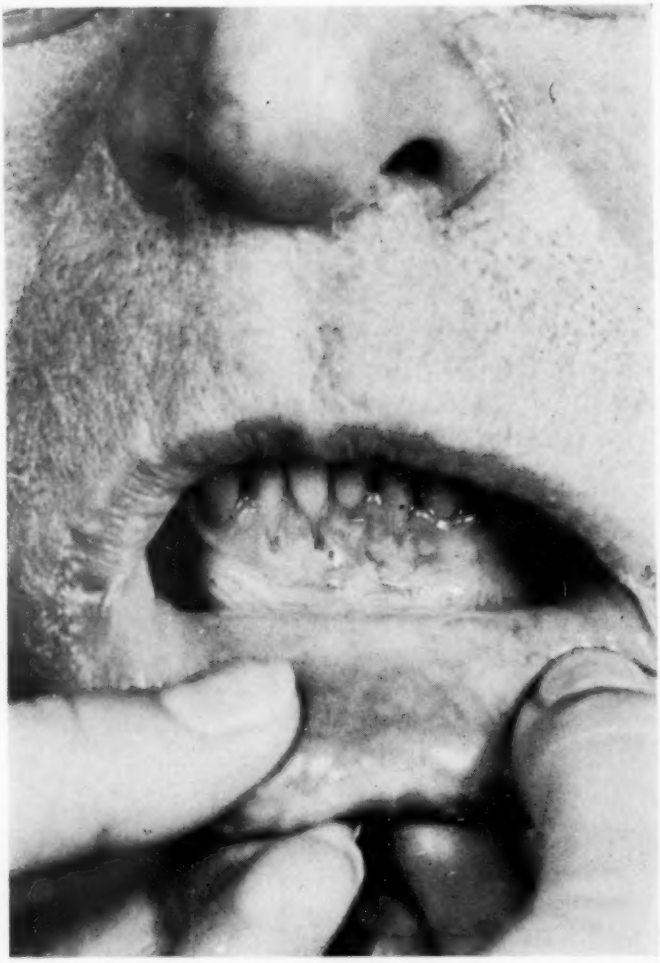

FIG. 2. Areas of leukoplakia in the sulcus and on gums, located at this man's favorite site for holding his quid.

site to which he had shifted his snuff, and which he had used for the last seven years. Again the squamous carcinoma was treated successfully with a radium mold. Despite contrary advice, the patient insisted on snuff-chewing and shifted his quid-site to an anterior position; recently a third carcinoma developed and the patient (Fig. 3) returned for confirmation and treatment!

In such instances the elusive factor of organ susceptibility probably is ex-

tremely important. Now that cancer cures are more common, the occurrence of subsequent cancers of the same tissue is increasing. Noteworthy is the seemingly more frequent observation of multiple primary carcinomas of the breast, stomach and colon.

No discussion of the relation between oral carcinoma and the use of tobacco would be complete without reference to the studies on betel-nut or buyo chewing. Unfortunately, the earlier reports did not include the information that tobacco was a common ingredient of the betel-chew.

Orr (6) has summarized much of the literature and has added several pertinent observations. Apparently the incidence of oral carcinoma among betel chewers

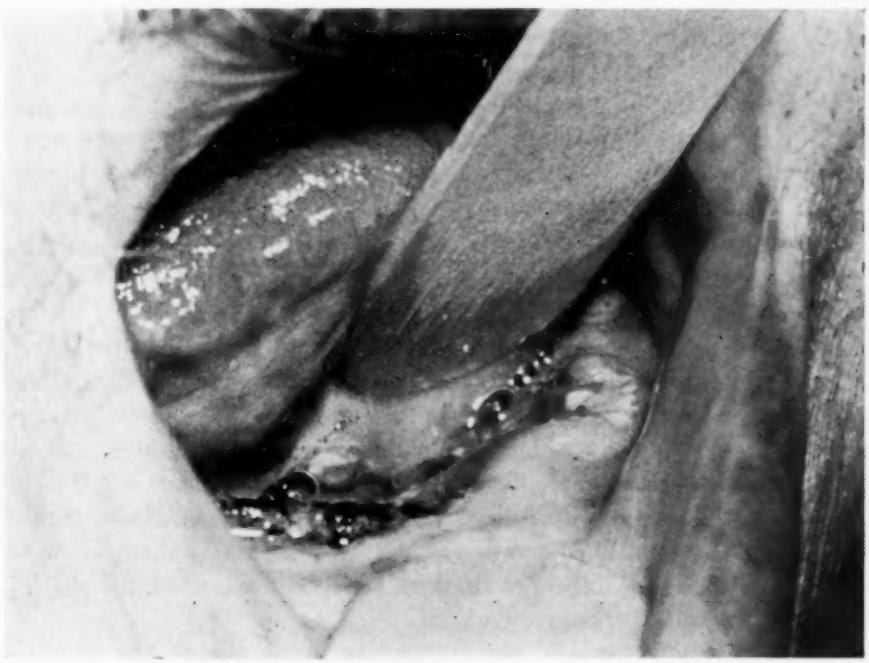

FIG. 3. Snuff particles are seen in and on the substance of this man's cancer of the lower alveolar ridge. Adjacent whitish areas are leukoplakia (and early carcinoma). Note exposed mandible to the left—the site of previous cancer at quid site, which was treated with radium-mold.

varies considerably in different districts. Orr correlates the higher incidence of malignancy found in southern India with the addition of a cheap, coarse tobacco and a strong alkali (shell lime) to the betel nut. He also suggests that the supplementary element of severe dietary deficiency may be a co-carcinogenic influence.

Interestingly, other clinicians have reported a low incidence of oral carcinoma among betel-nut chewers (12, 13). These discrepancies which are not unexpected when one considers that the lack of accurate and comparable statistics may be due, in part, to differences in the contents of the "chew." It would seem that experiments to find susceptible animals, and then to test the betel chew, are indicated.

Smoking

Among the more comprehensive studies of smoking habits and cancer is the report of Hoffman (14). Only his references to the incidence of oral lesions among smokers are pertinent to this essay; unfortunately his questionnaires did not include data concerning the use of chewing tobacco among the subjects studied. Suffice it to say that the results of his survey revealed that 79.2 per cent of the group were smokers, and of those with cancer of the buccal cavity, 83.3 per cent were smokers; this is not a significant difference. Among heavy smokers there was a greater incidence of persons dying of buccal carcinoma. Hoffman points out that deaths from buccal cancer are rare among the Chinese (2.3 per cent of cancer deaths), but very high in Cuba (14.6 per cent) and Mexico (13.8 per cent) where the incidence of heavy smoking is high. Again it should be pointed out that his figures do not include the use of chewing tobacco.

In the United States the incidence of buccal carcinoma has not increased appreciably, in contrast to the meteoric rise of lung cancer. As previously mentioned, reports suggesting an association of cigarette smoking and cancer of the lung are extremely interesting as regards the overall view of the carcinogenicity of tobacco, but they are not directly relevant to this study.

Experimental studies

Many investigators have attempted to produce carcinoma of the skin in various experimental animals with tobacco preparations and distillation products (15–17). Although cancers and precancerous lesions have been reported, in the main these studies have been inconclusive and the presence of an identifiable carcinogen has not been confirmed. It is pertinent to point out that in most of these experiments the tobacco products were applied *to the skin* rather than to the organs presumably affected, *i.e.*, the mouth and lungs. No significant numbers of cancer of the fingers of smokers have been reported, nor do skin cancers seem to develop in tobacco workers.

At present, various workers are attempting to duplicate the conditions in human smokers by the use of smoking machines (18) and direct application of the tobacco products to the tissues under experiment.

In this laboratory, pouch animals such as the golden hamster are being used to test possible carcinogenic effects of tobacco, by placing tobacco suppositories in their pouches for long periods of time, with replacement at intervals (19). Control suppositories of inert materials and of various foodstuffs are also being tested. To date, no tumors have been found in these animals but in view of the long exposure necessary to provoke malignant lesions in human beings it may take over a year before definitive results are obtained. Unfortunately, this particular animal may not be susceptible to the carcinogen; therefore, many other species will have to be investigated in the same manner. For example, we hope to use monkeys in such experiments.

Finally, one component of tobacco, arsenic, which has received special attention and which has been proved carcinogenic under certain conditions (20)

deserves further mention. Several authors have suggested that an important carcinogenic factor in tobacco might be arsenic. Our studies of the arsenic content of tobacco show considerable variation in different samples of even a single brand and show significantly high "contamination" with arsenic in common brands. Arsenic excretion in a heavy chewer was not found to be abnormal.

The possibility of an allergic phenomenon being a factor in the intraoral cancerous response to stimulation by tobacco should not be overlooked. Skin sensitivity tests with a few preparations from tobacco products have given no significant results in our hands. Similar materials have been procured for testing in the near future the possibility of an intramucosal sensitivity response, in persons suitable for such a study.

SUMMARY AND CONCLUSIONS

1. A preliminary statistical analysis of white males over 50 years of age who were seen and interviewed in the University of Minnesota Hospital suggests that the habit of chewing snuff or tobacco for more than twenty years is significantly associated with the occurrence of leukoplakia and cancer of the buccal mucosa, floor of the mouth, and the alveolar ridges. Cancer of the lip and face are also associated with this habit but to a lesser degree.

2. Pipe smoking and cigar or cigarette smoking are not significantly associated with the development of intraoral cancer.

3. Experimental methods of testing the possible carcinogenicity of tobacco and its products are outlined.

4. Brief mention is made of the possible importance of arsenic in tobacco.

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CLINICAL SHOCK

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Shock is part of a chain of events which often leads to death, and therefore is a matter of vital concern in the care of all who are seriously ill or injured.

HISTORICAL BACKGROUND

The term "shock" was first employed clinically in 1743 by the French surgeon LeDran (1): "The Bullet thrown by the Gun powder acquires such rapid force that the whole Animal Machine participates in the Shock and Agitation." Thus the syndrome acquired a name, but in subsequent years our concept of shock has changed considerably and has passed through many stages.

Not too long ago some (2) thought that shock was related to primary failure of the vasomotor center of the brain. Since in medicine, theory often determines practice, stimulants were the recommended treatment. There is no reason to suppose that this treatment, founded on a false premise, in any way benefited the patient.

More recently others (3, 4) have implicated a condition of toxemia, although the exact toxin involved has remained a matter of dispute. The toxic concept, despite attractive features, has so far failed to provide useful information for practical application. The outcome of this concept in terms of treatment was exsanguination-transfusion; this was a heroic measure which probably did the patient no good. Other hypotheses have been propounded from time to time, such as vasomotor exhaustion (treated by vasoconstrictors (5, 6)), fat embolism to the medulla (7, 8), acapnia (9), and others—some helpful, others fruitless, none a complete answer to the problem.

In recent years a new concept of the shock syndrome has evolved, namely, the mechanical concept, which offers a valid basis for practical and effective therapy: it works.

According to the mechanical concept as developed by Blalock (10), Phemister (11) and others, shock is a complex syndrome characterized by reduction in the effective circulating blood volume. As now visualized, shock is an acute, dynamic, labile process, always changing, never static, posing only two alternatives—recovery or death. The outcome can be influenced by appropriate therapy which, applied in time, will help to return the organism to that resilient internal environment (12) which we call homeostasis (13)—good health.

PATHOLOGIC MECHANISMS IN SHOCK

The circulatory system composed of heart, arteries, capillaries, veins and blood, when reduced to its essentials, may schematically be represented by only

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four main components (Fig. 1.): the heart, the arteries (represented by a single artery), the capillary bed (represented by a few capillary loops in blown-up scale, connecting a single arteriole and venule) and the veins (represented by a single vein). In this simplified scheme, with each component represented in a different scale, the direction of the blood flow is clockwise, from the heart, through the arteries, into the capillary bed, and through the veins to the heart

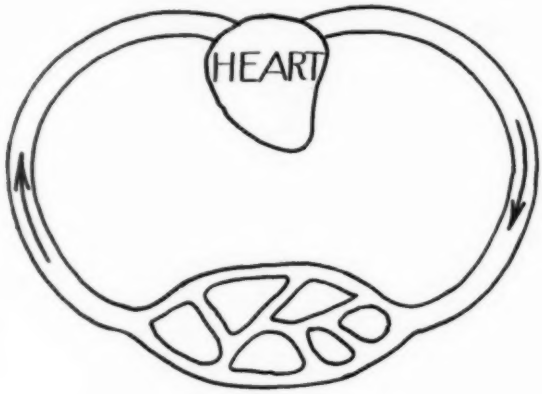

FIGURE 1

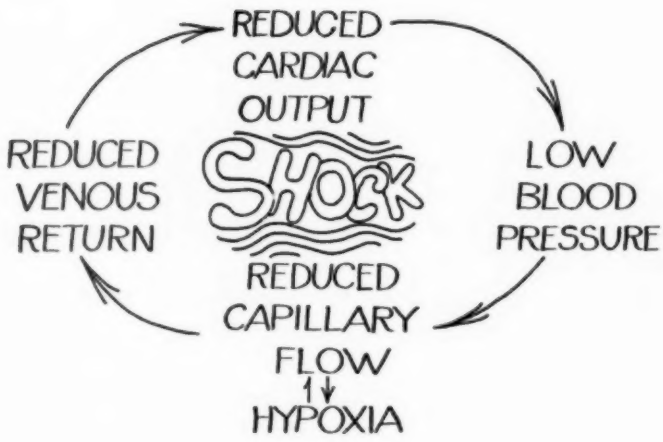

FIGURE 2

again. These four main components cooperate in their common work of supplying oxygen to the body tissues and removing the waste products of catabolism.

Loss of whole blood or its chief components, or loss of, or damage to any part of the circulatory system introduces the same chain of events (Fig. 2.): decreased effective circulation, reduced oxygen supply to the tissues, hypoxia, and anoxia. Shock is a vicious circle. If not arrested, the end result is always the same. The exact process may vary, depending upon the cause and the main physiologic derangement involved.

CLASSIFICATION OF SHOCK

For purposes of simplification, shock may be classified into four types (Table 1):

1. Oligemic, caused by reduced total blood volume, however brought about.
2. Propulsive failure of the heart or arteries, resulting in a reduction of arterial flow.
3. Venous pooling, caused by obstruction of a major blood pathway anywhere between the venules and the left auricle.
4. Capillary dilatation, when for any reason capillary tone is lost.

In shock these derangements may be combined and, in addition, aggravated by the contributory factors of heat, cold, pain, fatigue, hunger, fear or rage, thus producing shock of mixed origin.

Each of these four basic types of shock may initiate the same chain of events (Fig. 3). Each produces the same end-result. Sooner or later in the development of shock the heart receives less blood; the heart puts out less blood; arterial pressure falls; the arteries supply less blood to the capillaries; and less oxygen reaches the tissues. If the process is not reversed, hypoxia progresses to anoxia. Starved tissue cells undergo irreversible changes; asphyxiated capillaries permanently lose their innate contractility. Once this critical point is reached, the process of dying cannot be halted, even with renewed oxygen supply. Finally the heart, also starved for oxygen, ceases to beat.

Although each of these four types of shock is characterized by the same vicious circle and has the same end-result, each has a different origin and each requires a different treatment (14).

Oligemic shock will be discussed in some detail in order to illustrate principles, most of which pertain to the other three categories of shock, *viz.*, propulsive failure, venous pooling and capillary dilatation.

1. Oligemic shock

There are as many causes of oligemic shock as there are ways of losing blood volume. The most obvious is evident hemorrhage from an open wound. Less obvious is loss of blood volume in the case of closed fractures or crushing injuries in which both whole blood and plasma enter the tissues through the damaged capillary walls. Most difficult to detect is hemorrhage within a body cavity, which may occur where there is no external sign of injury, as for example, in the thorax from a lacerated intercostal or internal mammary artery, or in the abdomen from a ruptured liver, kidney or spleen. In any of these conditions the patient may lose blood fast enough to induce oligemic shock.

Although oligemia is common in traumatic injuries, it is also found as a result of hemorrhage in certain diseases such as bleeding peptic ulcer, ruptured esophageal varices, pulmonary tuberculosis, and in pathologic conditions associated with childbearing, such as ectopic pregnancy.

Oligemia is also common to all afflictions in which large amounts of plasma-like fluids are lost. Examples are burns, casualties from vesicant war gases, and peritonitis.

TABLE 1

Classification of Clinical Shock

OLIGEMIA
- Whole blood loss
  - hemorrhage, acute
    - evident or concealed
    - from injury or from disease
- Plasma loss
  - severe capillary damage
    - burns
    - vesicants
    - peritonitis
    - irreversibility?
- Water and electrolyte loss
  - dehydration
    - vomiting
    - diarrhea
    - fistulae
    - diuresis
      - diabetic acidosis
    - perspiration
    - deprivation of water
  - heat prostration

PROPULSIVE FAILURE
- Myocardial
  - insufficiency
    - infarct
    - hypoxia
    - overload
    - inflammatory and toxic
      - diphtheria, etc.
  - arrhythmias
    - fibrillation, flutter
    - paroxysmal tachycardia
    - heart block
    - neurogenic reflexes—"primary shock"
      - vasovagal, vagovagal
      - carotid-sinus syndrome
      - syncope
      - traction on mesentery
- Valvular acute destruction
  - surgical or traumatic
  - acute endocarditis
- Aortic
  - dissecting aneurysm

VENOUS POOLING
- Intravascular
  - mesenteric or portal-vein thrombosis
  - pulmonary embolism (in part)
- Vascular
  - reflex spasm in pulmonary embolism

TABLE 1—*Continued*

Extravascular
- tourniquet too loose (usual in first aid)
- vena-cava ligation
- sigmoid volvulus
- pericardial tamponade
- tension pneumothorax (contributory factor)
- prolonged Valsalva maneuver
- mediastinal encroachment
  - air, fluid (contributory factor)

CAPILLARY DILATATION
- Vasomotor interruption
  - spinal cord injury
  - spinal anesthesia
- Vasomotor inhibition
  - overexposure to elements
  - application of heat
  - certain drugs
    - vasodilators
    - general anesthesia
  - autonomic manipulation?
- Vasomotor paralysis
  - peripheral anoxia
    - tourniquet shock
    - thawing
    - advanced shock, regardless of cause, leading to irreversibility
- Mechanism uncertain
  - overwhelming infection
    - hemolytic streptococcus
    - gas gangrene
    - meningococcemia
  - also oligemic
    - peritonitis
    - acute pancreatitis?

COMBINATIONS OF THE ABOVE DERANGEMENTS

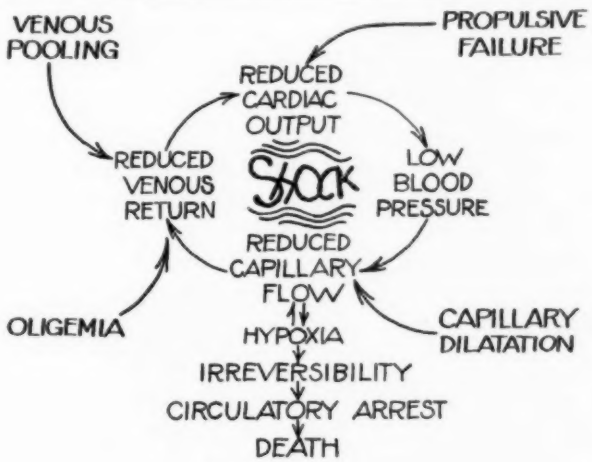

FIGURE 3

Oligemia occurs during surgical operations principally from blood loss, but additional contributing factors include dehydration by loss of water and electrolytes from the skin with perspiration, from the air passages and the wound.

Dehydration during anesthesia does not usually contribute greatly to oligemic shock; ordinarily little fluid should be lost. However, with certain diseases, loss of water and electrolytes will precipitate oligemia. Such conditions include severe staphylococcus food poisoning, cholera, acute bacillary dysentery, typhoid, and related acute intestinal infections and obstructions. Loss of fluid from vomiting, diarrhea and intestinal fistulae may be sufficient to induce oligemic shock. In obstruction of the gastro-intestinal tract excessive secretion of fluid, as well as retarded absorption, occurs proximally to the obstruction. Such fluid may or may not be vomited. If pooling of body fluid in the dilated gastro-intestinal tract takes place, the loss may not be recognized.

Similarly, in diabetic acidosis, loss of fluid through diuresis may produce the same effect. Individuals lost in the desert or on the sea, suffering from prolonged lack of drinking water and dehydrated, require replacement of body fluids. In such cases oligemia results from loss of water and electrolytes.

In burns, the capillaries, damaged by the heat, lose their semipermeability and leak a plasma-like fluid in which the smaller protein molecules of the albumin fraction predominate. The burned part swells as the fluid enters the interstitial spaces and is lost to the circulation. In addition, some fluid is lost through the burned surface of the body. In extensive burns, not only is the total blood volume reduced, but at the same time loss of plasma causes an increase in red cell concentration in the circulating blood. As plasma is lost the blood becomes thick and viscous and moves sluggishly in its passage through the vascular system. Thus its function of oxygen transport is impaired. In dehydration, due to whatever cause, with loss of water and electrolytes as in burns, oligemia is complicated by hemoconcentration.

Physiologic mechanisms

Against these varied insults to the circulation the body responds with several reactions which tend to sustain the circulation and maintain oxygenation (Table 2). In every case the same defenses operate, irrespective of the initial cause of the oligemia. They operate throughout the course of the shock process until circulatory equilibrium is re-established. They start early—almost immediately after the initial physiologic derangement appears.

Neurovascular reactions. The first of the mechanisms to enter the picture may be called neurovascular. They are reflected in the patient by pallor, cold skin and usually, but not always, rapid pulse.

For example, in a patient bleeding from a major vein, the reduced venous return causes nerve impulses to be sent from the right auricle of the heart to excite the vasomotor center in the medulla. As a result of this excitation the heart rate accelerates and peripheral vasoconstriction takes place. At the same time the fall in arterial pressure resulting from the decreased cardiac output excites the aortic and carotid-sinus pressure responses, causing speeded heart action,

vasoconstriction and secretion of epinephrine. The epinephrine, acting directly on the end organs, reenforces the effects of the vasomotor nerve impulses. Activation of the sympathico-adrenal system, involving all these changes, also contracts the arterioles of the peripheral tissues and viscera less sensitive to irreversible damage by hypoxia, reducing the blood flow in the periphery and shunting blood to the vital organs.

The total effect of these neurovascular responses is to maintain circulation in the vital organs despite reduced blood volume.

TABLE 2

Physiologic Mechanisms in Shock

NEUROVASCULAR
McDowall auricular reflex
Carotid sinus
Aortic pressor center
Sympathico-adrenal
constrictions
dilatations
tachycardia
perspiration
shunts
BIOCHEMICAL
Decreased basal metabolic rate
Accelerated coagulability
Hyperglycemia
Nonprotein-nitrogen retention
Increased blood lactic acid, pyruvate, amino acids, inorganic phosphorus, potassium, carbon dioxide, ketone bodies
Tendency toward acidosis
OSMOTIC
Hemodilution
decreased red cell count
hemoglobin concentration
hematocrit
plasma-protein concentration
increased plasma volume
HEMATOPOIETIC
Platelet liberation
Polymorphonuclear leukocytosis
Erythrocyte regeneration

Biochemical changes. Next there occurs a series of biochemical changes. The first are a decrease in the body's metabolic rate and an increase in the blood coagulability. These are obviously defensive. At the same time there are other developments such as hyperpotassemia, accumulation of lactic acid in the blood and mild acidosis. With these later changes, the defensive role is uncertain.

Osmotic mechanisms. As soon as there is a drop in the capillary pressure a third process begins. A change in the osmotic balance in the capillaries draws upon the fluid in the tissues to replenish circulating blood volume. In every capillary there

is a continuous exchange of fluid through the capillary wall (Fig. 4.). Two forces are at work:

1. Hydrostatic pressure, forcing fluid out of the capillary into the surrounding tissue space.

2. Osmotic pressure of the plasma proteins, drawing fluid into the capillary from the tissue spaces.

The hydrostatic pressure is higher in the arteriolar and lower in the venular end of the capillary, whereas normally the osmotic pressure is practically equal in both ends. Thus, at the arteriolar end, hydrostatic pressure forces fluid out into the tissue space while, at the venular end, osmotic pressure draws fluid back into the capillary. This process produces a balance of fluid exchange out of, and into the capillary.

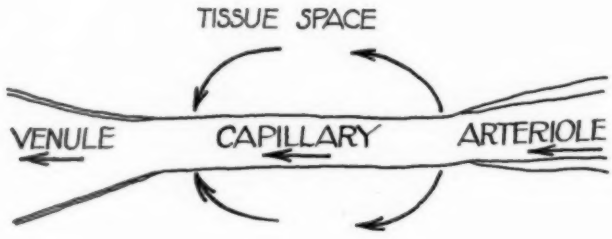

FIGURE 4

However, with reduced blood volume and arteriolar vasoconstriction, the hydrostatic pressure in the capillary falls. As a result, less fluid is forced from the arteriolar end of the capillary into the tissue. Meanwhile the osmotic pressure remains unchanged and continues to draw fluid from the tissues into the venular end of the capillary. The total effect is an increase in the fluid entering the capillary from the tissue, an increase in the effective circulating blood volume, and thus an increase in the effective blood circulation.

The neurovascular, biochemical and osmotic defenses start early and continue as long as there is a significant blood volume deficit.

Hematopoietic responses. A fourth group of changes occurring consequent to hemorrhagic oligemia involves the hematopoietic system. Within a half hour following acute hemorrhage there is an increase in platelets and, within an hour, in white cell production. Not until about four days later does the effect of red blood cell regeneration appear in the circulating blood.

Viewing on the one hand the defensive reactions of the body, and on the other the pernicious changes taking place in oligemic shock, it is obvious that the outcome depends greatly upon which factor predominates. So long as the defensive mechanisms counterbalance the deteriorative processes, blood pressure is maintained and the patient is said to be in a state of latent shock.

When, despite the body's defenses, the unfavorable processes prevail and blood pressure falls, the patient is in frank shock. It is at this point that vigorous

treatment is vital. Correct treatment, vigorously applied, will usually reverse the degenerative processes and restore the flagging defenses.

If, despite proper treatment, oxygen supply is not restored in time and anoxia causes cellular changes in the vital organs and capillaries from which they cannot recover, then shock is said to be irreversible. Correct treatment must precede the onset of irreversibility; otherwise the patient dies. The time factor is of the utmost importance.

Principles of management

Whatever the cause or type of shock, the principles of clinical management are the same: When shock is apparent,

1. Discover the cause
2. Determine the physiologic disturbance
3. Arrest the cause
4. Correct the physiologic disturbance
5. Combat hypoxia

For example, in traumatic oligemic shock, the cause is usually obvious. As soon as possible, arrest the cause. If the cause is bleeding, stop it without delay. Simultaneously correct the physiologic disturbance. In oligemic shock, lost blood volume must be restored. Treatment must precede irreversibility. If lowered blood volume is corrected in time, anoxia will not supervene. With massive blood deficit, replacement must be in terms of quarts rather than of pints—sufficient at least to restore the blood pressure to the normal range for that particular patient.

Blood pressure, pulse volume and skin color are basic indices for restored circulation, restoration indicating disappearance of the physical findings which originally signalized the onset and paralleled the development of the shock process. Since oligemia is a manifestation of depleted blood volume, replacement of blood volume is a specific requirement. The amount of blood lost determines the amount to be replaced. Thus, in oligemia, correction of the basic physiologic disturbance is in itself a method of combatting hypoxia. However, shock is a dynamic, ever-changing process, and to arrest the cause (or causes) in a patient requires continued observation and diagnosis.

The clinical manifestations of oligemic shock are of one pattern, regardless of the cause; hence, the clinical picture of shock is no guide to the etiology. Any one of a number of causes may produce the same clinical picture.

For instance, in a case involving concealed internal bleeding, a complete diagnosis cannot always be made immediately. Slow but persistent bleeding, as from a ruptured spleen, may not be recognized for some time. With continued bleeding the degree of progression and severity of latent shock is difficult to evaluate, until a fall in blood pressure marks the transition to unqualified shock. Even when shock is apparent, it may not be possible without careful observation (*e.g.*, intraperitoneal hemorrhage) to make a diagnosis complete enough to point out the cause which needs to be arrested. When the cause of the shock has been

arrested and the physiologic disturbances corrected, careful observation and continued restorative therapy will speed the patient's convalescence.

In massively bleeding peptic ulcer, the cause is an eroded artery. Prompt and certain remedial treatment is surgery. Until the bleeding is stopped, correction of the physiologic manifestations of oligemia is attempted by massive transfusion. The fluid replaced should be the same as the fluid lost, and the quantity equal to the quantity lost.

In burns, the diagnosis is obvious. The thermal trauma ceases before the patient reaches the doctor. In burn shock the essential physiologic disturbance is reduced blood volume by loss of plasma through the damaged capillary bed. This may continue for a day or two, but may be impeded in the extremities by pressure dressings applied to augment hydrostatic pressure in the tissues around the damaged capillaries and all capillaries peripheral to them. Since the oligemia in burns is associated with preponderant loss of plasma, the urgent need is for administration of plasma or a plasma-volume expander with colloid osmotic properties, in order to restore blood volume and thus correct hemoconcentration. Anemia, which may also develop, is a problem for later treatment.

In dehydration, dry mucous membranes and loss of skin turgor point to the cause—a loss of water and electrolytes, which results either from an increased output, a deficient intake, or both. The physiologic disturbance is corrected by restoration of blood volume with water and electrolytes, until hydration is reestablished. The sodium ion is of special significance in this connection.

2. Propulsive failure shock

In propulsive failure the cause of shock is a reduction in arterial outflow induced by defective pumping action of the heart and aorta. There are as many causes of propulsive failure as there are conditions interfering with arterial flow. Defective heart action producing shock may result from primary impairment of cardiac output due to inadequate contraction or defective rate or rhythm. Shock due to obstruction of arterial flow may result from aortic occlusion by a dissecting aneurysm.

Whatever the cause of propulsive failure, the result is the same. The blood flow from the arteries into the capillaries is diminished.

Effective defense mechanisms against acute propulsive failure are few. Since blood flow is primarily decreased by the condition, sympathico-adrenal activity is of little benefit, except for the dilating effect on the coronary arteries (which improves circulation to the cardiac muscle) and the shunting effect consequent to peripheral vasoconstriction (which diverts blood to the heart and brain). With only these limited defenses to rely upon, early treatment is particularly important in order to avert the progression from reduced circulation to hypoxia, irreversibility and death.

In all cases of propulsive failure, diagnosis is important, not so often as a prerequisite to removal of the cause, but more often in attacking the physiologic disturbance. In some cases the cause cannot be corrected during the shock phase.

Luckily, supportive measures which relieve the physiologic deficit, hypoxia, are helpful in tiding the patient over, despite damage to the propulsive mechanism.

For example, in an elderly patient with cold, moist extremities, dizziness, pallor, cyanosis, anxiety, faint heart sounds, feeble pulse, hypotension and a picture of physical collapse, the existence of shock is apparent. Complaints of precordial pain, dyspnea and fear of death make one suspect heart disease—the physiologic disturbance being propulsive failure. More detailed evidence, such as an electrocardiogram showing low voltage and notching of the QRS complex, lead one to a diagnosis of bundle-branch block from a probable myocardial infarct due to coronary occlusion. Removal of the cause is impossible. Correction of the physiologic disturbance, propulsive failure, likewise may be impossible except by means of the next step in management, *i.e.*, combatting hypoxia. Given such a situation, in which the demand for oxygen exceeds the supply, the demand can be reduced by narcotics given to relieve pain and promote mental tranquillity, and by sedation and rest to reduce the metabolic rate and thus the oxygen requirement. Administration of oxygen under pneophore pressure, if indicated by pulmonary congestion, will increase the supply.

3. Venous-pooling shock

There are as many causes of venous pooling as there are obstructions to the blood flow between the capillaries and the left auricle. In shock from venous pooling the obstruction prevents the blood in sufficient quantity from reaching the left side of the heart. In venous pooling, whatever the cause, the physiologic disturbance is the same. Blood collects in the affected veins and in the capillaries leading to them. Arterial blood enters the vascular bed, but its exit is impeded, and less blood reaches the heart. Cardiac output diminishes and arterial pressure falls. The circulation in the capillaries is inadequate. Hypoxia, unless relieved, progresses to irreversibility and death.

The natural defense mechanism of sympathico-adrenal activity may go into effect, contracting the peripheral arterioles, dilating the coronaries and speeding the heart, but this is of slight and temporary value. Though it raises the arterial pressure for a time, it does not prevent further pooling.

Unless early and specific treatment precedes irreversibility, with the natural defenses generally ineffective, hypoxia progresses to death.

To illustrate: a patient is brought in with pallor, cold hands and low blood pressure. Shock is apparent, so it is important to discover the cause. The patient complains of nausea and a severe, steady, lower abdominal pain for four hours. The abdomen is distended, tympanitic and tender; rectal examination discloses dark blood on the examining finger; and peritoneal tap produces pink fluid. X-ray examination shows dilatation of the colon proximal to the sigmoid. The diagnosis is sigmoid volvulus. The physiologic disturbance is the venous pooling in the twisted loop. Removal of the basic cause by surgery will at the same time arrest progression of the physiologic disturbance. Until and throughout surgery, hypoxia is combatted by giving oxygen. In venous-pooling shock, removal of the cause

is frequently surgical. If surgery is successful, it simultaneously corrects the physiologic disturbance and reestablishes the integrity of the circulation.

4. **Capillary-dilatation shock**

In the normal circulation, capillary tone is maintained partly by tonic vasomotor nerve stimuli. If, for any cause, this vasomotor nerve supply is interrupted, capillary tone is lost. The arterioles and capillaries relax and become engorged with blood. Vasomotor nerve impulses may be interrupted by spinal cord section or by spinal anesthesia. They may be inhibited by general anesthesia, drugs, exposure to extremes of weather, or application of external heat in a misguided attempt to give first aid.

In a case with the phenomenon known (by hindsight) to have been irreversibility, despite replacement of far more than the normal blood volume, it seems apparent that capillary pooling has been so extensive as to eliminate adequate venous return of blood to the heart.

Whatever the cause of capillary-dilatation shock, the effect on the circulation is the same. Blood stagnates in the smaller blood vessels, and venous return is diminished. Reduced cardiac output follows, and arterial pressure falls. Oxygen does not reach the tissues. Unless the process is arrested, hypoxia progresses to irreversibility and the patient dies.

If vasomotor nerve supply is interrupted, by the very nature of the disease the defensive vasoconstrictive sympathetic nerve reflexes are ineffective. If capillary contractility itself is impaired, in addition, the humoral vasoconstrictive defense by epinephrine is lost.

Since few of the natural defense mechanisms are effective, the patient is largely dependent upon treatment. As always, treatment must precede irreversibility.

In capillary dilatation, the clinical picture of shock differs from that found in the other three categories. Because of mental languor, physical collapse and low blood pressure, a diagnosis of shock seems appropriate. Despite this, the extremities are warm, dry and cyanotic rather than pale, cold and clammy.

If the cause is vasomotor nerve interruption by a high spinal cord section, that lesion is not susceptible to relief by treatment; but the physiologic disturbance, peripheral capillary dilatation below the level of section, can be corrected sufficiently by vasoconstrictive drugs to tide the patient over until vascular tone is reestablished by lower centers. Simultaneously one should combat hypoxia by giving oxygen, especially when respiratory nervous impulses have been interrupted by the trauma, in which case artificial respiration is also indicated. Blood transfusion may be of help in maintaining blood flow in the disproportionately large vascular bed.

CONCLUSION

When the basic principles of shock management are followed conscientiously, the chain of events which leads to irreversibility and death can usually be prevented or interrupted and reversed. Such knowledge has made it possible for modern surgeons to perform very extensive, prolonged surgical operations upon patients of all age groups without development of shock.

Whatever the cause of shock, management based upon a correct understanding of its varied mechanisms will usually remove the cause, correct the physiologic disturbances, combat hypoxia and restore the patient to homeostasis.

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VAGINITIS IN THE MENOPAUSAL AND POSTMENOPAUSAL WOMAN

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This paper deals with our experiences and impressions concerning vaginitis in the menopausal and postmenopausal woman. The material upon which it is based consists of 752 patients seen and studied at the Vaginitis Clinic, Jefferson Medical College Hospital from January 1, 1948 until January 1, 1953, a period of five years. During that period of time 1,113 patient visits were made. Approximately 26 per cent of the patients were over 40 years of age and 14 per cent were over 50.

THE VAGINA

Structure

The vagina is a flattened but distensible, epithelial-lined musculomembranous canal extending from the uterine cervix above, to the vulva below, with a course generally downward and forward. In the mature woman the anterior vaginal wall averages about 7 cm. in length, and the posterior wall, 8.5 to 9 cm. (1). In the process of aging, both length and volume may decrease by approximately one half. During the childbearing era, rugae are found, especially along the anterior and posterior walls. After the menopause these disappear and the mucosa becomes dry and glistening with scanty secretion. In addition, the fornices are gradually obliterated and the canal becomes less elastic, this being more noticeable at the vulvar end. From secondary infection, adhesions may form.

The proximity of the external vaginal orifice to the urethral and anal orifices need only be mentioned to call to mind how easy it must be for material from either to cause vaginal contamination.

Histology and cytology

Vaginal *histologic structure* varies greatly in different periods of life, fluctuating with the estrogen activity. The epithelium is relatively thicker when estrogen levels are high as at birth, during active menstrual life, and especially so during pregnancy. Three layers of the epithelium are usually recognized: 1) a basal or deep layer, 2) an intermediate layer of varying thickness, and 3) an outer or superficial layer. Various further subdivisions are favored by other authors (2). The vaginal mucosa of the sexually mature adult is composed of some forty-five to fifty-five cell layers, whereas that of the postmenopausal woman tends to show fewer cell layers. The underlying connective tissue layer of tunica propria becomes more fibrous in character as aging proceeds. Decrease in water and fat is also apparent. On the other hand, just as the postmenopausal endometrium

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may not always be atrophic, neither may the vaginal mucosa, and numerous variations occur.

Vaginal *cytology* has become increasingly revealing and important in recent years. Here again the role of estrogen is a paramount one. After a few weeks, when the newborn child has destroyed and excreted the maternal dowry of estrogen which it received through the placenta during intrauterine life, the smear shows evidence of atrophic change, *i.e.*, small, round basophilic cells, leukocytes and mucus. Cells from more superficial layers appear with the gradual assumption of estrogenic activity during the prepubertal years. During menstrual life, cyclic changes occur which, although not marked, are well known (3). There are even some cyclic changes in the postmenopausal epoch (4). In general, however, the cytologic picture in the menopausal and postmenopausal woman returns to that of childhood, with basal and intermediate cells predominating.

The finding of a definite estrogenic effect in cells of the superficial layer requires explanation in a postmenopausal woman. Some women normally lose ovarian function slowly; in others the adrenal gland may be implicated as a source of estrogen. Exogenously administered estrogen must also be considered. Feminizing ovarian tumors of theca-cell or granulosa-cell origin are possible. Vitamin A deficiency (5), procidentia and inflammatory changes may also produce cornified cells and a pseudo-estrogenic effect.

Biology

A discussion of vaginal biology is essentially a discussion of four subjects: epithelium, glycogen, acidity and bacterial flora, since it is mainly on these four factors that vaginal health depends.

As mentioned previously, growth of the vaginal *epithelium* is mediated through the ovarian hormones, particularly the estrogens. It is not definitely known whether the stimulus to cellular proliferation is a direct or indirect effect, since some substances termed proestrogens must be first absorbed into the circulation before exerting their influence (6). Progesterone has little effect on growth but does cause regression of cornification after estrogen priming (7). In large doses, however, some degree of vaginal epithelial proliferation and cornification can be induced with progesterone in the castrated and postmenopausal woman, but this result is not nearly so marked as with estrogen (8). Testosterone in average doses causes thinning of the epithelium, but some degree of vaginal epithelial growth can be induced with larger doses (9). The role of vitamin A deficiency has been mentioned; it is usually thought to be related to hypochlorhydria. In vitamin B deficiency a hyperestrogenic state may arise from inadequate estrogen inactivation. Vitamin C has also been considered by some to have a part in maintaining the vaginal epithelium at the menopause and thereafter (10).

During sexual maturity the vaginal epithelium is rich in *glycogen*, especially in the intermediate layer. Glycogen is deposited in the cells under the influence of estrogen and is easily demonstrated by Best's carmine method or more simply by Mack's iodine-vapor cytologic smear technique (11). Surprisingly, it is not demonstrable in cell-free vaginal secretion. In our experience glycogen content

is roughly proportional to alkaline phosphatase content demonstrated by histochemical methods (12). The mechanism of the deposition of glycogen is unknown, but it is probable that glucose diffuses into the basal layer and is then converted into glycogen. The glycogen content is not influenced by the factors affecting hepatic content, since neither starvation nor administration of thyroxine leads to any appreciable change in concentration (13). Following the local or general administration of estrogenic hormones, glycogen reappears in the estrogen-deficient vaginal mucosa.

Vaginal *acidity* is generally conceded to be due to lactic acid, which is a catabolite of glycogen. The mechanism of this process is under dispute. The various theories have been reviewed by Rakoff *et al.* (14). The pH of the normal vaginal secretion generally is about 4.0 to 5.0. It is lowest during pregnancy; with the decline of ovarian activity in the postmenopausal era it tends to rise, although neutrality is only occasionally attained. If the vagina becomes alkaline with a pH greater than 7, it is usually the result of bleeding or infection. There is some correlation of pH and flora, the lowest pH values being in patients with grade I flora. Acidity can be measured with an indicator paper such as nitrazine, or more exactly with a glass electrode. Our determinations have been with the latter method.

The vaginal flora varies in different periods of life and depends upon the glycogen and estrogen present, plus the vaginal acidity. The classification based upon the presence of Döderlein's bacillus (Lactobacillus vaginalis) proposed by Schröder (15) is most generally used:

Grade I: Döderlein's bacillus alone.

Grade II: Döderlein's bacillus with other type(s) of organisms.

Grade III: Only non-Döderlein bacilli.

The grade of flora can easily be determined by the Gram stain and is a rough index of the state of vaginal health. Vaginal infections are associated with grades II and III. During the postclimacteric era conditions become less and less favorable for the growth of Döderlein's bacillus, but we have found them on occasion in women over 60 years of age. Needless to say, the administration of estrogen to postmenopausal women tends to improve vaginal flora.

SYMPTOMATOLOGY OF VAGINITIS

Leukorrhea. This is the most common symptom of vaginitis. Its causes in the older woman are outlined in Table 1. It may be watery or purulent in character and is frequently malodorous; at times it is bubbly or blood-tinged. Its exact source may not always be clear but the clinician should recall that it may arise from structures both above and below the vagina.

Bleeding in the older woman, especially if postmenopausal, is a significant symptom, since in more than one third of cases cancer is the cause (16). The bleeding may be slight and attributable to atrophic vaginitis or a cervical polyp. If malignancy is not to be missed, however, curettage and biopsy are necessary.

Pruritis is an important symptom. In a previous report (17) we found that approximately 40 per cent of our patients in the clinic complained of it. The sensa-

tion varies and may be compared with a tickle, with a pricking sensation or with the feeling of something crawling over the skin. Although pruritus is more commonly associated with vulvar disease, vaginal disease is a significant factor. A psychogenic background is not unusual.

Dyspareunia is less a complaint of the older woman than of one in the childbearing era; but since coital activity does not cease with menstruation, it is sometimes a complaint associated with vaginitis. It may vary from severe pain due to inflammation or kraurotic changes, to a mild discomfort due to "dryness."

TABLE 1

Causes of Leukorrhea in the Older Woman

1. Benign cervical disease
   Polypi, erosion, eversion
2. Infections
   Bacterial—pyometra, tuberculosis, "nonspecific"
   Protozoan-Trichomonas vaginalis
   Fungous—Monilia albicans
   Miscellaneous—lymphopathia venereum, granuloma inguinale
3. Mechanical causes
   Pessaries, foreign bodies
   Pelvic relaxations, prolapse
4. Estrogenic variations
   Hypoestrogenic—atrophic
   Hyperestrogenic—endogenous (*e.g.*, feminizing tumors), exogenous
5. Chemical causes
   Irritating medications or douches
6. Genital tumors
   Benign
   Malignant
7. Systemic disease

DIAGNOSTIC MEASURES

History. In approaching the patient for a cataloguing of symptoms the physician should assume a serious and interested attitude, since the problems involved often seem extremely delicate to the patient. Especially is this true in the case of the spinster. On the other hand, there are those patients who have come to regard their symptoms as completely normal and therefore volunteer very few details of their exact character. A listing of previous therapies including douches is necessary, if only to learn what *not* to prescribe next. Previous operations may give important clues. Systemic diseases such as allergies, diabetes mellitus and blood dyscrasias may have vaginal implications.

Pelvic examination should never be omitted. It should be as complete and as thorough as one would perform for a suspected case of carcinoma. The patient should be told to refrain from coitus or the use of any vaginal medication including douching for forty-eight hours previous to the examination. The lithotomy position is most acceptable, but at times the knee-chest position is required in

order to visualize the cervix adequately. In virgins, a Kelly speculum can be used. In any event the examination should consist of the following: 1) inspection of the external genitalia, 2) testing for pelvic relaxation, and palpation of the Bartholin gland areas, 3) visualization of the cervix and vagina, 4) bimanual examination, and 5) rectal and rectovaginal examination. The inner aspects of the thighs and perianal areas should be carefully inspected. In the obese patient a certain amount of pigmentation and maceration is generally observed. Urinalysis (catheterized specimen) and proctoscopic examination are carried out when indicated.

Wet smear examination is indispensable for diagnosis in vaginal disease; yet this simple procedure is often omitted by the busy practitioner. It is performed by inserting a cotton applicator into the vagina, gathering posterior fornix secretions and then dipping the applicator into a few cubic centimeters of physiologic salt solution. The specimen should be studied at least within an hour or so. From the number of leukocytes present it is possible to gauge the degree of infection. Trichomonads—protozoans slightly larger than a white cell and exhibiting independent motility—are easily seen. Monilia with its bamboo-like branching and buds is often found; if the smear is too thick, 10 per cent potassium hydroxide will help to delineate them. With experience, Döderlein's bacillus may be detected. The cytologic state with respect to estrogen effect is easily noted and with a special stain (18) a rapid determination of ovarian function can be made.

Stained smears and cultures are occasionally indicated. We use them in vaginitis studies, usually to determine the grade of vaginal flora. The gonococcus, Vincent's organisms, and Hemophilus ducreyi are discernible by Gram staining but these are rarely found in the later years of a woman's life. Cultures are at times necessary. The method used may be routine, aerobic or may employ special media for gonococci, tubercle bacilli or fungi.

The *vaginal pH* is more of academic than practical interest in the management of vaginal disorders. As mentioned previously, special indicator papers or a pH meter may be used for this purpose.

The utilization of the *Papanicolaou* smear in older women has been reviewed in another paper from this institution (19). At least three smears should be obtained on each patient: 1) vaginal (aspirated from the posterior fornix), 2) cervical (scraped fron the portio with a wooden spatula), and 3) endocervical and endometrial (aspirated with the use of a laryngeal-type metal cannula from the endocervix). From an obvious lesion, smears may be taken directly. In postmenopausal patients when the secretions are very thin or serous, a drop or two of Mayer's egg albumin may be placed on the slide in order to make the cells cohere. Aside from demonstrating both malignant and abnormal nonmalignant cells the smear denotes the degree of estrogenic activity, the effects of irradiation, and the presence of infection, bleeding, or cells arising from outside the genital tract. For purposes of investigation most of our patients in the Vaginitis Clinic are studied by this technique, since it is by this method that neoplastic lesions can be detected in their incipiency.

Biopsy of any chronic, localized vaginal lesion is always indicated. In the de-

termination of the type of vaginitis, biopsy finds its greatest sphere of usefulness in the diagnosis of the atrophic type, when smear information is indefinite. Various factors, such as glycogen or enzyme content, can be determined with special staining methods. Livingstone (20) reports that more than half of 108 patients with primary vaginal carcinoma were between 45 to 64 years of age, so this lesion should certainly be kept in mind in geriatric patients. We have also seen 2 cases of cervicovaginal granuloma inguinale and 1 of tuberculosis in patients over the age of 50.

Cervical biopsy and curettage are indispensable in the diagnosis of uterine malignancy, both forms of which (cervical or endometrial) may be manifested by blood-tinged leukorrhea. For reasons mentioned elsewhere (21), we subscribe to the opinion that histologic rather than cytologic findings of malignancy are necessary for diagnosis before therapy.

Miscellaneous procedures consist of *blood serology, darkfield illumination studies* and *skin tests*, as in the case of tuberculosis and lymphopathia venereum. It is wise to carry out urine and blood sugar determinations in cases of moniliasis. Hematologic investigation is at times required, in order to detect blood dyscrasias with vaginal manifestations.

THERAPEUTIC CONSIDERATIONS

Gynecologists differ greatly as to what constitutes *normal vulvovaginal hygiene*. In our opinion it should consist of frequent cleansings with a mild soap externally, followed by gentle drying of the parts. An occasional acid vaginal douche is indicated, especially in the presence of slight discharge. We advise lactic acid, since it is the normal acid of the vagina (one teaspoonful of lactic acid USP to two quarts of warm water). The douche is preferably taken in the supine position. The woman should also be advised that cleansing after stool is to be done, wiping antero-posteriorly.

In the presence of vaginitis, systemic measures should not be neglected. The general nutritional state should be improved, with adequate vitamin intake assured. Body rest is helpful since it also rests the local area. Improving the vaginal status is wise but it must be supplemented by specific measures for various infections. Simple procedures such as applications of very cold or very hot water, or compresses of witch hazel, relieve pruritic symptoms. The cervix should be made as normal as possible. Nearby structures such as the urethra and rectum must be examined and treated. Local therapy may be administered by insufflation, douching, or with tablets, suppositories or jellies. By roentgenographic means Rakoff and Casper found water-dispersible jellies to be superior, since spreading is rapid and a considerable portion remains in the vagina even after twelve hours (22). In trichomonal infections particularly, the marital partner should be investigated.

Therapy of the more common specific disorders

There are countless ways of treating the different forms of vaginitis. We shall consider those that we have most thoroughly evaluated and which seem to give

the best results in our clinic. The incidences of the three most important forms are tabulated according to age group in Table 2.

Atrophic vaginitis. This condition is sometimes termed senile vaginitis but the former term is preferable, since this type of vaginitis occurs, irrespective of age, in the surgically castrated woman, following irradiation, or as a result of various functional or organic states of the ovary. Grossly, the vaginal mucosa appears smooth and thin, and true ulceration may be present in severe cases. Telangiectatic areas which bleed on pressure are common. Kraurosis and leukoplakia vulvae often occur concomitantly. The symptoms of atrophic vaginitis are a thin, watery, occasionally bloody discharge, and pruritus. In our series the age in women without any artificial castration ranged from 40 to 81.

Changes in the vaginal biopsy specimen are indicated by a thin epithelium, perhaps only a few layers thick, often with sub-epithelial inflammation. Both wet smears and those for cytologic study show a preponderance of the basal-layer cells and leukocytes. In our patients, pH varied from 4.8 to 7.1 in 65 of the cases

TABLE 2

Incidence of the Three Main Types of Vaginitis in the Older Woman. Study Based on 128 Consecutive Cases

	Age 41–50	Age 51–60	Age 61 and over
Atrophic vaginitis	27 cases (50%)	32 cases (65%)	25 cases (100%)
Trichomonas vaginalis vaginitis	18 cases (33%)	10 cases (21%)	—
Monilial vulvovaginitis	9 cases (17%)	7 cases (14%)	—
Total	*54 cases*	*49 cases*	*25 cases*

in which it was measured; the average was 5.9. The flora was grade II in 17 of 59 cases examined (29 per cent) and grade III in the remainder (71 per cent). Both glycogen and alkaline phosphatase were scant. Monilia complicated one case (pH 4.8) and Trichomonas another.

Although estrogen therapy is almost specific, a buffered vaginal jelly (pH 4) usually suffices to allay symptoms, and has a salutary effect on vaginal cytology as well (17). Therapy in our cases consisted of the insertion of 5 cc. of jelly every other day for several months. Observations were made after one to four months of treatment (see Table 3). In mild cases general local hygiene with a lactic acid douche is sufficient for comfort. Sources of local irritation (*e.g.*, pessaries) should be removed and, in the presence of bleeding, there should be a search for carcinoma in the genital tract, according to the accepted procedures of diagnosis.

Trichomonas vaginalis vaginitis. Trichomonas vaginalis is a flagellate protozoan, slightly larger than a white cell, associated with a distinctive form of vaginitis. Although its pathogenicity has been questioned, Trussell and Plass (23) implanted pure cultures of from 200,000 to 2,000,000 organisms into 29 women:

9 became infected. The symptomatology varies a great deal but characteristically consists of a profuse, purulent, malodorous, yellow-green bubbly discharge, with pruritus and vaginal soreness. In the well established case, on examination the introitus is found to be reddened. The aforementioned discharge is present and there is a diffuse cervicovaginitis with small punctate areas of hemorrhage. The diagnosis is easily established by wet smear examination. In our series Trichomonas was the second most common cause of vaginitis in the postmenopausal group. This infection however tends to decrease as estrogen function wanes. It is for this reason that we feel that the administration of estrogen for Trichomonas in the older woman is irrational. Indeed we did not note any cases in women beyond the age of 60 (Table 1).

TABLE 3

Buffered Vaginal Jellies in the Treatment of Atrophic Vaginitis (55 Cases)

Therapy consisted of vaginal insertion of 5 cc. of jelly every other day. Patients were followed for one to four months. (Reproduced with permission of the publisher, from Lang, W. R., Rakoff, A. E., and Sosnowski, J. R.: Recent advances in the management of vaginitis, *in* Surgical Forum, Philadelphia, W. B. Saunders Co., 1952, p. 357).

	Before	After
	%	%
Discharge	60	42
Itching	14	9
Vulvar irritation	21	13
Wet smears (atrophic changes)	100	46
pH above 5	77	42
Flora (presence of Döderlein)	5	13
Estrogen effect (deficiency)	79	54
Biopsies (10 cases) (inflammatory changes)	70	20
Glycogen content (8 cases)	Scant, 100	Scant, 100

The epithelium is usually not affected histologically, although at times subepithelial infiltration with inflammatory cells may be seen and even ulceration may be noted. The organism may also be found by Gram stain and by Papanicolaou smear. In the latter, atypical cytologic changes caused by the trichomonad may lead to confusion with carcinoma in situ (24). Cultures are difficult. It has often been stated that trichomonads thrive in an alkaline vagina. If one arbitrarily classifies the normal vaginal pH as 4 to 5, then this is essentially correct (Table 4). There does not appear to be a close correlation of pH with the grade of flora. In the nonpregnant, more than half the time the pH is greater than 5. In our series, the average in women over 40 was 5.4.

The treatment of vaginal trichomoniasis is prolonged and vexing, with repeated recurrences after a "cure" has been obtained. Many hundreds of local agents have been proposed, including several of the newer antibiotics. We have tried terramycin suppositories with excellent results (17). However, without the addition of an appropriate fungicide, monilia infections are common. Such a combination of antibiotic and fungicide is now available and is under investigation. In

our experience therapeutic doses of the antibiotic given for other disorders have no effect on vaginal trichomonads. Yet it seems certain that a lasting cure of the disease must ensue from some preparation given orally or parenterally that will be absorbed into the blood stream and ferret out each trichomonad wherever it is hiding.

Drugs which we have found useful are a pentavalent arsenical (Devegan, Winthorp-Stearns), diodoquin (Floraquin, Searle) and silver picrate (Picragol, Wyeth). All of these except Picragol are in the form of tablets and may be used in conjunction with an acid douche for several weeks.

TABLE 4

pH and Flora in Trichomonas Vaginalis Vaginitis

(Data from 106 cases, grouped according to age)

	Age under 40, pregnant (32 cases)	Age under 40, not pregnant (51 cases)	Age over 40 (23 cases)
pH under 5	14 or 22.3%	19 or 37.3%	—
pH over 5	18 or 77.7%	32 or 62.7%	23 or 100%
Flora, grade II	22 or 69%	11 or 25%	5 or 21%
Flora, grade III	10 or 31%	21 or 75%	18 or 79%

TABLE 5

pH and Flora in Monilia Vulvovaginitis

(Data from 75 cases, grouped according to age. Two of the women over 40 were diabetic and 1 had been receiving estrogen cream locally.)

	Age under 40, pregnant (47 cases)	Age under 40, not pregnant (21 cases)	Age over 40 (7 cases)
pH under 5	26 or 55%	17 or 81%	4 or 57%
pH over 5	21 or 45%	4 or 19%	3 or 43%
Flora, grade I or II	36 or 76.6%	10 or 47.6%	5 or 71%
Flora, grade III	11 or 23.4%	11 or 52.4%	2 or 29%

Monilial vulvovaginitis. The fungus most commonly infecting the vagina is Candida albicans, known usually as Monilia. The symptoms are slight discharge of a highly acid and watery nature, severe pruritus, and vulvar irritation with edema. The vagina and cervix are inflamed and show typical cream-cheese patches. It is common in pregnancy and in diabetes and at times is the first inkling of either. It is an infrequent but troublesome complication of estrogen therapy in the menopause, and of therapy with the newer antibiotics administered locally or systemically. In the male it is much less frequent than Trichomonas. When found in the older woman, the fasting blood glucose level should always be determined.

Like trichomonads, the organisms are found by wet smear examination (10 per cent potassium hydroxide may be added, to rid the field of debris). They are also detectable by Gram stain and by Papanicolaou smear. With Monilia infection the vaginal pH and flora, even in the older woman, approach those of the childbearing era (Table 5). We have very rarely seen the conbination of atrophic

vaginitis and clinically significant Monilia infection in either clinic or ward practice.

Treatment is satisfactory with either a gentian-violet jelly (Gentia-Jel, Westwood) or a higher fatty acid such as propionic acid (Propion Gel, Wyeth) (17). Either is administered daily by a measured dose applicator for two weeks; then every other day for several weeks. An alkaline douche, such as two tablespoonfuls of baking soda to two quarts of cool water, is often soothing. The parts should be kept dry.

Nonspecific vaginitis. This refers to a diverse group of infections in which no specific organism can be found. Not only is a grade III flora present but there are definite signs of infection clinically. The atrophic vagina is particularly susceptible to this type of vaginitis. It also follows cervical cauterization, conization, or dilation and curettage. Treatment is based on local hygiene, and sulfonamide creams (Triple Sulfa Cream, Ortho). In postmenopausal women with leukorrhea associated with a variety of saprophytic organisms, a buffered acid jelly (such as Aci-Jel, Ortho) is frequently helpful. In those patients in whom the vaginal membrane is particularly atrophic, the use of an estrogen-containing cream (Dienestrol, Ortho) is useful in building up a thick vaginal membrane with a healthy vaginal flora. Since some of the hormone may be absorbed from the vagina it should not be used in patients in whom there is any contraindication to estrogen therapy.

SUMMARY

1. Normal vaginal structure and biology are outlined, with special reference to the older woman.

2. The symptomatology of vaginitis, and diagnostic measures are reviewed.

3. Both general and specific modes of therapy in various forms of vaginitis are considered.

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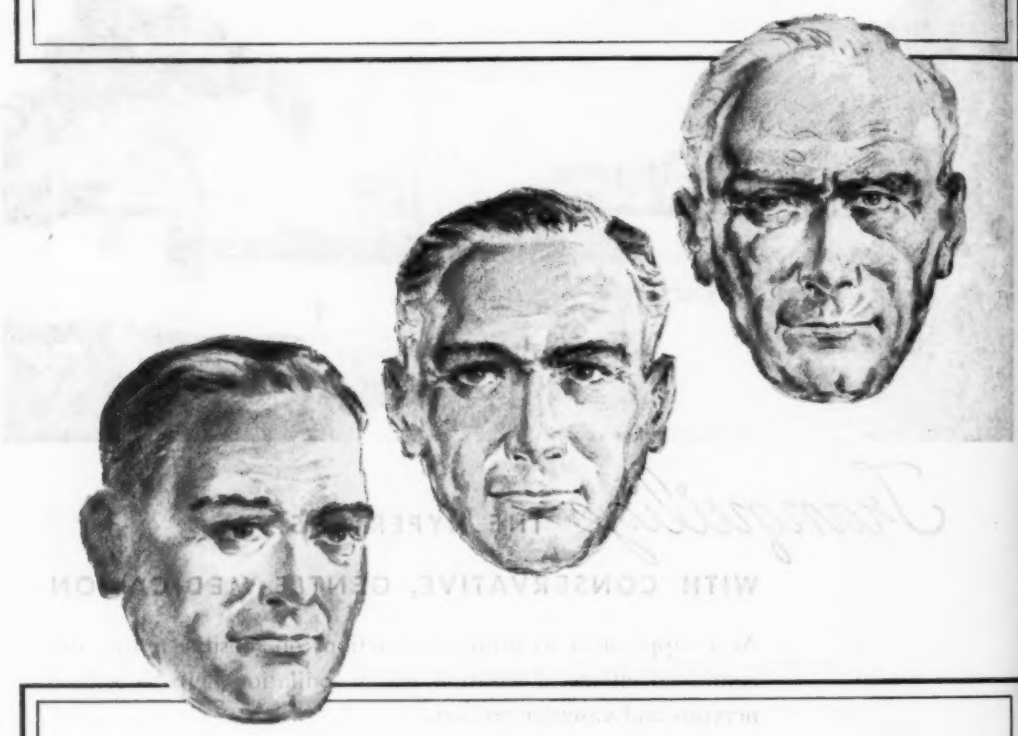

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